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CLINICAL AND EXPERIMENTAL ALLERGY

A CRITICAL REVIEW OF THE MECHANISM AND TERMINOLOGY OF ALLERGY*

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IN THE whole realm of immunology there is no other subject more confused by a multitude of terms, definitions, and conflicting opinions than that commonly designated as anaphylaxis, allergy, hypersensitiveness, idiosynerasy, atopy, etc. This, however, is but a natural and expected state of affairs in view of the frequency and diverse clinical manifestations as well as the practical importance of the subject and our lack of accurate information on the mechanism concerned. But I believe that enough acceptable data have now been accumulated to permit of at least a partial classification and house cleaning of terms and ideas; this would appear to be highly advisable and especially in so far as the rank and file of the medical profession are concerned, most of whom are now hopelessly confused.

In the first place what is the most appropriate term for designating the phenomena? It should be one covering two conditions: namely, (1) a state of exaggerated susceptibility to various substances harmless for the majority of individuals and (2) a state of reduced susceptibility usually acquired by repeated administrations of the noxious agents. The term hypersensitiveness, therefore, is unsuitable because it does not include the related state of hyposensitiveness; the same is true of idiosynerasy and likewise of anaphylaxis, since the latter means "without protection" and is an excellent term for designating exaggerated susceptibility but fails to include the reverse state of acquired tolerance. The term "atopy," the latest addition to the

*From the Research Institute of Cutaneous Medicine, Philadelphia. Address delivered before the American Association for the Study of Allergy, Minneapolis, June 11, 1928.

Read before the American Association for the Study of Allergy, Minneapolis, Minn., June 11, 1928.

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already topheavy list, means "strange disease" and all students of the subject certainly agree upon this point although Coca and Cooke proposed it primarily for hay fever and asthma in which heredity is a frequent and important factor.

The outstanding fundamental change would appear, therefore, to be a state of *altered reactivity* of the body cells which may be in the usual sense of exaggerated susceptibility or the reverse of reduced susceptibility or tolerance. Accordingly it would appear that the term "allergy" is most appropriate of all proposed for designating this broad and important subject, although it conveys no idea at all of the mechanism concerned but merely emphasizes the characteristic and outstanding change of an altered reactivity of body cells which in the usual sense is one of exaggerated susceptibility.

That immunity to diphtheria and other diseases also involves the questions of susceptibility and tolerance of body cells, that is, of a change in their reactivity is entirely irrelevant to the subject, as the mechanisms are fundamentally different with a complete independence of the true allergic phenomena from the ordinary bacterial antigen-antibody reactions as shown by Zinsser and his associates.

But if this is an acceptable term for the whole subject, upon what basis should subclassifications be made? Are we justified in classifying on the basis of being able or unable to demonstrate antibody in the blood? Or according to what is known of the chemical nature of the antibody? Or according to the influence of heredity?

I have long objected to any classification based upon our ability or inability passively to transfer the antibody and especially to guinea pigs and rabbits, because failure to do so could not be accepted as indicating the absence of antibody. Indeed only a few years ago it was believed that the allergic antibody to timothy and ragweed pollens could not be passively transferred to guinea pigs until this possibility was demonstrated by Walzer and Grove by improved methods. And now that we have the Prausnitz-Küstner method of passive transfer to human skins this objection would appear to be still further justified, since it has shown the presence of antibody in the serum of human beings with various allergies not only to horse serum but also to various pollens, pea and other foods, and to dandruffs and other exciting agents of asthma which could not be transferred to the lower animals. It is true, however, that all attempts to transfer passively drug, bacterial, and poison ivy allergies by the guinea pig and Prausnitz-Küstner methods have so far failed, but this does not necessarily mean that antibodies are absent. It may merely indicate failure to demonstrate their presence in the circulating blood. In such instances they may be attached to the sensitized cells as so-called "sessile receptors" as is apparently true at least in the case of tuberculin allergy. Indeed I believe it can be stated without reserve as a widely accepted fact that the allergic reaction is a cellular phenomenon and under the circumstances I see no escape from the possibility, and indeed the probability, that in some allergies the antibody is predominantly cellular with tuberculin hypersensitiveness as the type, while in others it is predominantly

humoral, with serum hypersensitiveness as the type, although we are totally unable to explain at present why there should be this difference in the distribution of the antibody. Possibly experiments consisting of the extraction of the sensitive epithelium of the skin of individuals with tuberculin, ivy, and drug allergies will demonstrate the presence of antibody in the cells and at any rate it cannot be said that antibody is absent; we are merely justified in stating that its presence in the blood has not been demonstrated. Therefore, my objection to any classification on this basis.

But may allergy be classified on the basis of the chemical nature of the exciting agent or whether or not it is antigenically active? Personally I believe that a classification on the basis of the chemical nature of the exciting agent is an acceptable one at the present time. And by this method we would have but two groups: namely, (1) those in which the exciting agent is known to be protein or closely related to it and including not only serum but the foods, dandruffs, probably the pollens, and even tuberculin and the products of other bacteria and (2) those in which the chemical nature of the exciting agent is unknown as in the case of the drug, poison ivy, and similar plants causing dermatitis venenata. It is true that the exciting agent of pollens and house dust have been regarded as being nonprotein in nature by Grove and Coca, Black and others, but more recent studies by Walzer and Grove have shown that some at least may be protein; a recent study in my laboratory with ragweed pollen has convinced me that this is a fact, while the work of Long and Seibert and of Zinsser and Tamiya have shown that the active substance in tuberculin and other bacterial allergies is a protein or closely related to it. Here again we must be very cautious in stating that the exciting agents of allergy are nonprotein on the basis of being nondigestible and nondialyzable when it is recollected how minute an amount of agent can elicit an allergic reaction and readily escape chemical identification. Indeed, I am fully prepared to see proved that the exciting agent of poison ivy is a protein or closely related to it and likewise in the case of quinine, morphine, belladonna, oils, balsams, resins and other drugs of vegetable origin although this possibility can be excluded in the case of arsenic, mercury, iron, coal tar derivatives and other metallic drugs unless they really do combine with body proteins to form an antigenically active foreign protein as originally suggested by Wolff-Eisner. The latter, however, has never been proved, but neither has it been definitely disproved. When one remembers that the predominant thought in the mechanism of parasitropism in chemotherapy involves a change in the chemical nature of arsphenamine and other compounds in the blood or other tissues following administration for the production of new parasiticidal compounds, it must be admitted that this idea of Wolff-Eisner's is not to be lightly thrown aside but wisely left open for future investigation. Indeed I know of no more important field for research in allergy than upon the mechanism of drug hypersensitiveness with special reference to the possible rôle of antibody and the chemical nature of the exciting agents.

Furthermore, the fact that a substance is unable to induce the production of demonstrable antibodies, like precipitins and agglutinins in the blood, that is, fails to be antigenically active in the immunologic sense does not necessarily mean that it is unable to induce allergic sensitiveness. It means nothing more than that it fails to produce antibodies in the blood but leaves wide open the possibility of producing antibodies attached to cells as in the case of tuberculin allergy. As a matter of fact I think it can be stated at present that there is no relation whatsoever between precipitins in the blood and the allergic antibody. Several investigators have shown that the antibody may be present in a sensitizing serum in which precipitins could not be demonstrated and that, conversely, sera containing large amounts of precipitin, like rabbit antiegg and rabbit antiragweed, were unable to produce allergic sensitization even by the sensitive Prausnitz-Küstner method, although it is possible that a repetition of these experiments with changes in technic may result in positive reactions. Also that the allergic antibody may be neutralized in the test tube without any visible precipitation or alteration in the specific activity of the latter as shown by Coca and his associates. So why make any classification on this basis? It is true that precipitin and allergic antibody are frequently present together, but in my opinion we may safely accept as a fact that they are not identical and that precipitin is unnecessary in the mechanism of allergy.

And was it necessary to coin the new word reagin for designating the antibody in hay fever and asthma in view of the already long list of names for the antibody concerned in the allergic reaction? Certainly the antibody in serum allergy may be acquired by immunologic stimulation and furthermore the so-called "reagin" concerned in the Wassermann reaction, which led Coca and Grove to adopt the term in relation to hypersensitiveness, is indeed an antibody of the kind active in the test tube even though without demonstrable effect upon Spirocheta pallida and probably heterophile in nature. Furthermore tuberculin and other bacterial allergies may be acquired by immunization as shown by Zinsser and his associates and the frequency with which the symptoms of hay fever and asthma first appear in adult life, the acquisition of primrose sensitiveness by Bloch, etc., has led me to the belief that these may be acquired by frequent contact with the exciting agents despite the negative outcome of animal experiments. Indeed I believe that altogether too much emphasis has been laid upon the outcome of experiments with guinea pigs and rabbits in studying this question of acquired allergic sensitization, since they are by no means as susceptible to either active or passive sensitization as are human beings except in the case of serum allergy.

Furthermore, I doubt the wisdom of insisting upon successful transfer of antibody by the Prausnitz-Küstner method as a criterion of asthma or other allergic states since the presence of free or circulating antibody need not be present if its cellular situation is the important change. In other words this test may have a greater positive than negative value, and in my opinion a

negative result is not acceptable as evidence of the absence of possible allergic sensitization due to a strictly cellular situation of antibody.

Indeed Fineman has expressed the opinion that the degree of sensitiveness of asthmatics is better elicited by skin tests than by determining the antibody content of the blood, although Levine and Coca have observed that skin sensitiveness in early and late hay fever bore a relation to the antibody content of the blood in almost all cases, and Clark and his associates have recently advocated the passive transfer method as being probably more reliable for judging the clinical severity and danger of serum allergy than skin tests. All of this leaves one with the impression that allergic sensitiveness may exist without demonstrable antibody in the blood and that while skin tests may be more valuable for diagnosis, the presence of circulating antibody may be more dangerous or at least more significant of acute and even dangerous sensitization in human beings.

This question of the relative clinical importance of fixed or cellular and free or circulating antibody, however, is still further complicated by the results of treatment of hay fever and asthma since there may be an increased toleration or amelioration of symptoms without appreciable decrease in either skin sensitiveness or of allergic antibody in the blood. This leaves us at present very much in the dark regarding the mechanism of desensitization, although I am confident that future investigations with more accurate methods will show a quantitative decrease of sessile or cellular antibody and fully justify the present use of the term "desensitization" as indicating a reduction of sensitization of body cells by exhaustion of antibody. It also leaves us in doubt about the meaning of the term "antianaphylaxis" which is applied to the refractory state supposed to be due to the presence of sufficient antibody in the blood to neutralize effectually small amounts of exciting agent or allergen in the blood before the latter reaches sensitized cells with the production of shock even though this circulating antibody may afford no protection against the local or topical application of the allergen to the sensitized cells of the skin or a mucous membrane. Since circulating antibodies have been found with such regularity in hay fever, asthma, and serum allergy by the Prausnitz-Küstner method without demonstrable protection of the affected individuals, it is apparent that the exact mechanism of this state and of nonspecific desensitization are as yet unknown and deserving of reinvestigation for elucidation.

And is a classification warranted on the basis of hereditary influence? No one can deny that heredity plays an important rôle in hay fever and asthma, but it must be remembered that it likewise plays an important rôle in infection and immunity to disease in general, as indicated by the clinical studies of Draper and Stockard and the laboratory studies of Lewis and Loomis in tuberculosis of guinea pigs whose work has indicated a possible correlation between antibody production and allergic irritability.

In the first place what is the nature of this hereditary influence? All that is definitely known is that the majority of cases of hay fever and asthma have one or more antecedents with some type of recognized allergy and that there

is transmitted a tendency to develop allergic sensitiveness of some kind without, however, any direct transmission of any particular allergy by either mother or father, although Clark, Donally and Coca have recently stated that the offspring of hay fever subjects are more likely to suffer from hay fever than bronchial asthma, and the reverse. Does this mean the transmission of a particular tissue or shock organ concerned in the production of allergic antibody? If so, it has not been demonstrated or proved. Or does it mean the transmission of a peculiar tendency or facility for producing the antibody, that is to say, of tissues tuned up as it were for the production of the antibody? This likewise is unproved, although a far more attractive thought and possibility. Or does it mean the transmission of a peculiar sensitiveness to the effects of allergy as I proposed in 1923? This, too, has not been proved, but I believe the possibility is worthy of consideration and study.

From the clinical standpoint I have always been impressed with the importance of vasomotor instability or irritability in hay fever, vasomotor rhinitis, asthma, and other human allergies. These individuals blush very easily and are sometimes very sensitive to changes in temperature, scratches, etc. Furthermore, it is commonly and widely accepted that vascular changes, and especially dilatation, congestion and edema, are the outstanding and prominent tissue changes because the allergic shock organ or tissues in human beings is largely involuntary muscle. Under these conditions it is reasonable to believe that individuals with sensitive vasomotor systems, that is, individuals who show an exaggerated tendency to localized or generalized vasomotor disturbances would be more susceptible to the effects of allergy than the more stolid individuals who possess less sensitive vasomotor systems and are less sensitive to vasomotor disturbances. In my opinion the transmission of an unduly sensitive vasomotor system to any irritant or emotion is the hereditary factor in allergy and that it is possible that many human beings actually acquire allergic sensitiveness as to milk for example, without showing signs or symptoms simply because they are less susceptible to the effects of allergic shocks. Certainly human beings are much more susceptible to allergy than the lower animals and are much more likely to develop or present vasomotor disturbances. Furthermore, young children are much less likely to show hay fever and asthma than adults, and it is well known that they have better balanced vasomotor systems. Moreover, hay fever and asthma are less commonly observed among negroes than among whites and they, too, as a class have less sensitive vasomotor systems than the latter; and finally, hay fever, especially, is more likely to occur among high-strung individuals of both races than among the more stolid and lowly. All of this has led me to regard a sensitive vasomotor system as the hereditary factor, not with any peculiar or specific relationship to allergy, but simply one of greater susceptibility to the effects of allergy because smooth muscle and particularly the smooth muscle of blood vessels happens to be an important shock organ in human allergic reactions. I have no objection to the coinage of atopy as a special designation for those allergies in which heredity can be traced, because all

allergies are indeed strange diseases, but I think it was uncalled for in an already overburdened nomenclature and especially since more intensive studies may show a similar influence of heredity in more clinical types of allergy than are now surmised.

These considerations led me in 1923 to propose in the third edition of my book on *Infection, Immunity and Biologic Therapy* (page 598) a classification in which the whole group of phenomena were designated under the common term of allergy with two subgroups: namely (1) those allergies caused by protein-exciting agents or those closely related to proteins and which in the light of our present information may include natural and acquired serum sensitiveness, hay fever, most forms of asthma, tuberculin, and other forms of bacterial sensitiveness and (2) those caused by drugs of nonvegetable origin, possibly ivy sensitiveness, and other forms of dermatitis venenata if it is finally proved that the exciting agents of the latter are toxic glucosides and definitely non-protein in nature. If, however, it is subsequently shown that drugs and ivy form protein compounds in the tissues, this classification would be unnecessary and any further classification be for clinical purposes and convenience only in the way of giving separate names for clinical entities of basically similar mechanism. I see no reason at present for abandoning this classification; indeed and on the contrary, I believed that the results of investigations since 1923 have still further shown that it is both reasonable and substantially correct.

It may be that in the future we shall remove drug allergy altogether from the group of allergic conditions since it is included now almost solely by reason of the fact of its resemblance to allergy but with almost no further justification in view of our present information on its mechanism. Indeed, we commonly overlook the fact that drug sensitiveness and tolerance may be more of a pharmacologic than an allergic problem and more than enough harm and confusion have been done in medicine by the power and tyranny of analogy. For example, in chemotherapy we have more than begun to abandon the theory of chemoreceptors of Ehrlich, proposed to explain organotropism or toxicity for the body cells and parasitropism or toxicity for the parasite on the basis of the existence of hypothetic specific side chains or receptors analogous to the obsolete side chain theory of immunity. Rather I am personally in favor of placing the whole business upon a definite chemical theory in which the chemical compound does or does not combine with body cell or parasite, according to whether the protoplasm of the latter does or does not contain chemical constituents of physiologic importance possessing a combining affinity for the chemical compound or medicament. It may be that in so-called drug idiosyncrasy the body cells happen to contain naturally or acquire as the result of former administrations more of the chemical constituent possessing an affinity for the drug than the body cells of the average and majority of individuals without involving the question of possessing a superabundance of theoretic chemoreceptors; and that acquired drug tolerance is not a matter of exhaustion of receptors or allergic antibody but merely a matter of exhaustion of the chemical constituent of the protoplasm having this combining affinity for the chemical agent or

drug. If this mechanism is finally proved, the drug idiosyncrasies and tolerances could be removed from the category of allergy, but in the meantime we may leave it in this group with the idea in mind that it is possible that a protein exciting agent is produced by union of drug and body proteins, that an allergic antibody to this drug-protein antigen is produced which is entirely cellular in situation and that drug tolerance involves a mechanism of exhaustion of this cellular antibody in the same manner as is probably operative in the desensitization to other allergies caused by agents of known protein constitution and mediated by demonstrable antibody.

In conclusion I believe that in the interests of orderliness and clearness it is possible, advisable, and permissible to get rid of many terms which now contribute so materially to confusion and with this in mind I advocate the adoption of a simpler terminology as follows:

1. To employ the term *allergy* and abandon that of anaphylaxis, hypersensitiveness, idiosyncrasy, and atopy.

2. To designate the exciting agent as *allergen* and abandon the terms anaphylactogen, sensibilogen, sensitinogen, and atopen.

3. To base classification upon what is known of the chemical nature of the exciting agent and drop classifications based upon the success or failure of demonstrating antibody in the blood by passive transfer of sensitization to guinea pigs or human skins or according to success or failure of active sensitization of guinea pigs. Or to base it upon a division into clinical types, as the dividing line between acquired and natural allergies is too poorly defined for classification on these grounds as is likewise a division into so-called normal and abnormal allergies.

4. To designate the antibody as *allergin* or allergic antibody and abandon the terms anaphylactin, sensitizin, reaction body, albuminolysin, precipitin and reagin.

5. To adopt the cellular theory in its essentials as the underlying mechanism and abandon the humoral and related theories.

6. To adhere to the terms active and passive sensitization because less cumbersome, more euphonious and better known than the term allerization.

7. To adhere to the term desensitization for expressing a decrease of symptoms under therapeutic intervention as a result of increased toleration for the exciting agent even though its exact mechanism is unknown.

It seems to me that this simplified nomenclature is quite sufficient for present purposes, at least until it is proved that the phenomena in man and in the lower animals involve separate and distinct mechanisms with different kinds of antibody. But in my opinion this has not yet been proved, and I believe the term allergy is ample for designating the phenomena as a whole, as likewise the term allergens for designating the wide variety of exciting agents, allergin for the antibody, etc., as long as we have reasons for believing that the mechanism of serum allergy in the guinea pig is fundamentally the same as serum allergy, hay fever, asthma, etc., of human beings.

THE POTENTIAL ASTHMATIC*

By F. M. Pottenger, M.D., Monrovia, California

CLINICAL PICTURE OF ASTHMA

WHEN one sees a patient suffering from a paroxysm of asthma the dyspnea as a rule overshadows all other symptoms. On examining the patient, however, if the case is severe, the physician notes a rapidity of heart action, a cyanosis, a diminished respiratory excursion, a tense emphysematous chest moving in the inspiratory phase. Râles and rhonchi are heard of a character more or less distinctive, which, together with the particular character of the respiratory murmur with its prolonged expiratory phase have come to be recognized as making up the asthmatic type of breathing. If the attack is severe and prolonged, the heart may be enlarged and show signs of embarrassment. There may be a considerable or a small quantity of sputum. Eosinophilia is usually present. The condition may have developed suddenly or slowly.

HOW DOES ASTHMA EXPRESS ITSELF?

Asthma expresses itself in the neurocellular mechanism of the bronchus as a contraction of the smooth musculature, an exudation into the tissues, and an increase in bronchial secretion. This we at once recognize as a vagotonic or parasympathicotonic picture.[1]

The neurologic picture, however, is not dependent on nerve stimulation alone. There is a primary cellular element in every physiologic or pathologic action, which of course is modified by various hormones as well as the nervous system. Biophysicists have proved that nerve action depends upon the physical state of the cell; its degree of alkalinity or acidity; also, its content as well as that of the surrounding fluids in substances such as nutritive materials, cholesterin, hormones and various electrolytes such as *Ca, Na, K. P,* and *Mg.*[2, 3, 4, 5]

It is further shown that the vagus which is the parasympathetic component of the vegetative system, concerned in the production of asthma, is closely associated in its action with the *K* of the cell. Without *K* there can be no normal parasympathetic action. In parasympathicotonia we have a tendency to deficiency of blood calcium and excess of blood potassium, with alkalosis and increase of blood phosphates.

Asthmatics are very apt to show endocrine disturbances, particularly that of hypo-adrenia, hypothyroid, hypoparathyroid, and hypogonad, and the thymicolymphatic state.

The vagus is opposed in its action in the bronchial musculature by the sympathetics, which are linked up in their activity with the *Ca* of the cell.

*Read before the Sixth Annual Meeting of American Association for the Study of Allergy, Minneapolis, June 11-12, 1928.

Therefore we have two antagonisms in the normal or physiologic function of the bronchi; the sympathetic and vagus nerves in the correlating mechanism; and the *Ca* and *K* of the cell in the production of the fundamental activities of tonus and rhythm.

We have a third antagonism of a chemical nature: the H and OH of the tissues. These also align themselves as antagonists, the H with the sypmatheties and *Ca*, and the OH with the vagus and *K*.

Like all schemes of action these are subject to variability and, at times, effects the reverse of what are expected are observed. There are times when stimulation of the vagus nerve may produce acceleration of the pulse and when an increase in *Ca* may be followed by a parasympathetic instead of a sympathetic effect; so these antagonisms must not be accepted as universal and unalterable, but rather as being the usual relation, the one met most often under normal circumstances.

That asthma is a local parasympathetic syndrome cannot be questioned. That it is often met in individuals who show universally increased parasympathetic tonus or parasympathetic syndromes in certain organs other than the lungs is also well known. Bradycardia, epiphora, vasomotor rhinitis, hay fever, nasopharyngeal catarrh, spasmophilia, hypermotility and hypersecretion of the gastrointestinal canal, spastic constipation, mucous colitis, diarrhea, shell-fish poisoning, urticaria, angioneurotic edema, eosinophilia, digestive hypoglycemia and hypotension are found frequently in the group of patients to which asthmatics belong.

CAUSES OF ASTHMA

In our discussion of the cause of asthma we must approach it from a double point of view; first, that of the potential asthmatic; and second, that of the precipitating factor.

A certain percentage of people, so-called constitutional arthritics, are potential asthmatics at birth, and as soon as they contact stimuli which are directed toward the pulmonary parasympathetic neurocellular mechanism, they may develop the asthmatic syndrome. Many such individuals develop asthma soon after birth, others, in the early years of life. There are still others who, although they have a very unstable equilibrium between the sympathetic and parasympathetic bronchial neurocellular mechanism, yet, under ordinary circumstances remain free from asthma. When subjected to unusual parasympathetic stimulation, however, members of this group, too, may develop the asthmatic syndrome. During childhood such individuals often are subject to colds, sneeze on slightest exposure, are subject to hay fever, laryngitis, spasm of the glottis, and bronchitis. Slight colds may be accompanied by sonorous râles in the chest. These conditions are at once recognized as being of a catarrhal congestive and exudative type such as has been suggested as belonging to the exudative diathesis. Many of these individuals during childhood, as well as in later years, are subject to eczema and urticaria. These, with other parasympathetic syndromes previously mentioned, make up a distinct type of vegetative imbalance which belongs to the vagotonic constitution.

It seems that in the group possessing these particular constitutional characteristics, there occurs at times an incomplete elaboration of protein, which results in unmetabolized products gaining access to the blood and lymph streams, from which they are deposited in the skin and mucous membranes. These products possess the property of sensitizing tissues, and particularly of producing their effects upon the parasympathetic neurocellular mechanism. When the substances which have sensitized the cells again come in contact with them a reaction of hypersensitivity occurs. Such a reaction may appear as a vasomotor rhinitis, a hay fever, an asthma, a severe gastrointestinal disturbance, an urticaria, an eczema, a colloidoclastic reaction; or other syndromes which are less easily recognized.

Certain individuals of this group who are prone to asthma also seem to possess constitutional hepatic inadequacy. This is of great importance because of the detoxicating influence of the liver upon substances of alimentary origin. Such individuals show idiosyncrasy to foods and suffer from anaphylactic states more often than those with normal liver function. They also show hypoglycemia which aligns them with the vagotonic group.

Constitutional vagotonia, speaking of the condition as an inherited one is, as a rule, widespread although its manifestations may be confined to certain tissues or organs, so we must think of asthma as being a local manifestation of a more or less generally unbalanced neurocellular mechanism.

A hypersensitive neurocellular mechanism is not only prone to be rendered allergic to protein, but this hypersensitivity may be expressed in a heightened reaction to any and all stimuli. An instance of this is the vasomotor rhinitis which is associated at times with gastrointestinal disorders and with sexual congress, also asthma which results from reflex stimuli arising in other organs such as the nose, heart, gall bladder, gastrointestinal tract, and pelvic organs.

Hypersensitive tissues and organs also react readily to local stimuli of an irritating character and to general stimuli such as those of an emotional nature and those due to weather changes. The fundamental cause of the reaction in all of these conditions is not the particular exciting factor but the constitutional instability which makes the neurocellular mechanism hypersensitive to stimuli of many kinds. Therefore, antigens, chemical substances, changes in weather and reflex impulses acting upon hypersensitive cells produce paroxysms of asthma.

I personally had an experience which illustrates how local cells may become specifically sensitized. I have always been subject to vasomotor rhinitis and hay fever. One time I was taking a tablet of aspirin for headache. When I had chewed the tablet to a powder I was compelled to sneeze, and this forced some of the powder into my posterior nares. Almost instantly the tissues became edematous and closed the nares completely, a condition which remained for several hours. The edema was accompanied by a profuse nasal discharge. Since that time, whenever I take aspirin, a vasomotor rhinitis occurs. This condition is analogous to the specific allergic reaction which

follows the deposition of pollen in, the tissues of the mucous membrane of the nose in the production of hay fever, and the tissues of the mucous membrane of the bronchi in the production of asthma.

TREATMENT OF ASTHMA

If the conditions herein mentioned underlie asthma and hay fever, then one or more of the following therapeutic measures suggest themselves: first, to change, if possible, the parasympathetic neurocellular hyperirritability; second, to desensitize the cells if specifically sensitized; third, to remove the patients to surroundings which are free from substances to which they are sensitized, in case of air-borne stimuli, and to withhold from use by the patient foods or other substances to which they are known to be allergic; and, fourth, to remove known sources of reflex stimulation.

The success of desensitization of the body cells as a method of relieving asthma has been due in no small measure to the energy of members of this Society. Their individual contributions rank with the best that have been made to the subject. The administration of thyroid extract in certain instances, when a deficiency of this hormone was present has proved that in some instances the affection possesses endocrine aspects. The correction of reflex irritation arising in other organs has been successful sufficiently often to show this as a factor. The same may be said of climatic change.

All of these measures, however, leave much to be desired. They leave most patients still potential asthmatics, waiting for the proper stimulus to induce another attack. The probable reason for this is that they fail to change or correct the constitutional or acquired hyperexcitability of the bronchial neurocellular mechanism and so leave the patient in a condition to again become asthmatic when the exciting stimulus arises. Potential asthmatics possess different degrees of hypersensitivity. It is a common experience that some are much easier to relieve than others. Where the imbalance is very marked most measures have so far proved unavailing.

Could the tendency to congestion and exudation in the tissues be relieved and the constitutional parasympathicotonia be overcome, probably asthma and the entire group of allied hypersensitive conditions could be averted. So far, however, we do not know how to cure it, but we do know certain measures that improve the condition of the imbalance. Parasympathicotonia is not a matter of hyperirritability of the nerves alone. It is a complex condition in which the tissues which react with the parasympathetics also have a very important part. Relief of parasympathetic syndromes may be brought about by forces which depress parasympathetic nerve action, or by forces which stimulate the antagonistic sympathetic neurons; or, by decreasing the substances which are responsible for activity in parasympathetic structures, or by increasing the substances which produce inhibition in them.

In this connection hormones must be considered. The successful use of adrenalin in relieving asthmatic paroxysms proves its relationship definitely, but there are other hormones whose relationship to the sympathetic action is also very close, and which must be considered. Such are the thyroid, parathy-

roid, and testicular hormones. In appropriate cases hormones from these glands may be used advantageously for their therapeutic effect, along with other antiasthmatic measures.

Atropine is a substance which lowers parasympathetic activity, particularly that due to the vagus nerve. The cell acted upon by the nerves, however, is just as important in parasympathetic hyperactivity as the nerves themselves. These too may be influenced therapeutically, as is evident from the antagonistic action of *Ca* and *K* ions in the cells.

Calcium may be able to combat parasympathetic syndromes in several different ways. In tissues innervated by both sympathetic and parasympathetic neurons such as the pupil, the nasal mucous membrane, the bronchi, the heart, and the gastrointestinal tract, calcium acts with and fortifies sympathetic activity, and in so doing opposes the parasympathetic action. Calcium, further, has a property of allaying muscular hyperactivity as we see in tetany, and in spasms in various tissues. It further decreases the permeability of cell membranes, in which it antagonizes sodium and potassium. By so doing it decreases the tendency to exudation in the tissues.

Such effects should all be of value in influencing the underlying condition which is responsible for asthma. That *Ca* does have such effects is shown in many parasympathetic syndromes met in clinical practice. Its effect in relieving the intestinal spasm, productive of pain and diarrhea in tuberculosis of the bowel is well recognized. Its relief of urticaria and the anaphylactic phenomena accompanying serum reaction is often gratifying. In hay fever and asthma it will often give great relief.

A disappointing experience in the use of calcium is that one cannot always produce the desired effect in overcoming the spasm, even though its employment is based on sound physiologic principles. This, however, must be expected. Physiologic reactions differ from test tube reactions, in that there are often individual differences in patients and differences in the same patient at different times which interfere with always obtaining the same reaction following what seems to be the same stimulus. At certain times a reaction occurs directly the reverse of the one expected. Such has been noted by physiologists in experimental animals, where under certain conditions stimulation of the vagus produces acceleration of the heart instead of inhibition. In still other cases we may not be able to overcome the parasympathetic overbalance, no matter what remedy we use.

The employment of calcium has been considered of no avail by some because of the findings on blood-calcium estimation. Patients with asthma have been examined and found at times to have the usually accepted normal or even increased amounts of *Ca* in the blood. Again, it has been shown that after *Ca* administration, usually within three hours, the blood calcium returns to its former level. In regard to these observations it can be said that the normal *Ca* content of the blood varies under different circumstances and in different individuals. Environmental conditions undoubtedly cause variation in

the blood *Ca*. The amount of sunshine and seasons are known to influence it. So do various hormones. So must we expect a variation in the *Ca* content of the blood of asthmatics.

It is not the blood calcium alone that is to be considered but the K:Ca ratio; the relative tonus of the sympathetic and parasympathetic nerves; the hormone balance; and the H:OH ratio. Kylin[6] found on determining the *K/Ca* ratio of the blood of a large group of individuals that in normal persons the ratio is approximately 2, there being twice as much *K* in the blood as there is *Ca*. In asthmatics, on the other hand, the ratio was always high, running from 2.04 to 2.93, averaging 2.48. In only one case did it fall below 2.19.

Hetenyi[7] has shown that while the blood calcium attains a normal level within a few hours after calcium administration there is still a retention of about one-half of the *Ca* administered somewhere in the body tissues. Of 260 mg. administered, after three hours, there was still an increase of 6 mg. in the blood, while 35 mg. had been eliminated in the urine and 90 mg. in the feces. Thus 131 mg. could be accounted for, leaving 120 mg. unaccounted for but somewhere in the body. This indicates that a low serum-calcium content may mean either a reduction of body calcium or a storage in the tissues.

Calcium must not be administered in severe asthmatic paroxysms in the hope of relieving the paroxysm, as may be done by adrenalin, but for a slow change in cell activity. Its action may be increased by the simultaneous administration of atropine.

SUMMARY

1. There are two causes of asthma, the fundamental underlying cause and the precipitating cause.

2. Asthmatics belong to the constitutional arthritic class, and particularly to those of the exudative diathesis.

3. Asthma expresses itself as a local parasympathicotonia, usually in an individual who shows more or less general parasympathicotonic phenomena.

4. Constitutionally, asthma is associated with an overbalance of the parasympathetic nerves; an overbalance of *K* as compared with *Ca* in the cells; an increase in OH ions as compared with the H ions of the tissues; and a deficiency in certain sympatheticotonic endocrines, such as the adrenals, thyroid, parathyroids, and gonads.

5. Sensitization to food, pollens, etc., response to reflex impulses from other organs, also to chemical and mechanical irritation, and sensitiveness to weather changes, are only precipitating factors in a disorganized neurocellular mechanism.

6. Treatment must be directed not only to the relief of the precipitating cause but also to changing whenever possible the hypersensitive neurocellular mechanism.

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DISCUSSION

Dr. Warren T. Vaughan, Richmond, Va.—This paper should receive a lot of discussion. I feel that the Society is particularly fortunate to have such a paper to open the meeting with. We are prone to become rather one-sided in our outlook on the subject of allergy and to talk of it too much in terms of protein sensitization. So, for a keynote speech, we have a paper which says very little about protein sensitization.

We fail to recognize, or at least to emphasize often, that asthma is more or less of a chemical reaction in which two bodies react. It is not only the allergen which is responsible, but it is also the reacting body which is the human being. So we must consider both sides of the chemical equation.

I have a lantern slide. I want to bring out one or two points. Perhaps the first point is that in our discussions of the subject of immunology or allergy, we have so many different terms applied to one and the same phenomenon or process which makes it difficult sometimes for some of us to understand the other fellow's language. We talk about immunology, allergy, and atopy, and everyone has to slip in a new term. I have been guilty of attempting to slip in a new term myself, so I feel that I can voice the criticism.

(Slide: See chart in article on Rôle of Specific and Nonspecific Factors in Allergy and Allergic Equilibrium, Jour. Lab. and Clin. Med., April, 1928, iii, 633.)

This is a table which I have elaborated more for my own good than for anyone else, because I feel that I can visualize fairly clearly the underlying processes and can explain it to patients very easily with the help of this chart.

"The specific allergenic causes of allergy, and the nonallergenic causes." There is much that could be criticized in this chart, for example, as to whether bacteria are specifically allergenic or not; and in the second bracket we find the groups which Dr. Pottenger is speaking about particularly. He is talking about the type of individual. We must consider both the reacting body, the specific allergenic factor, and the individual. The second bracket, I feel, includes a great deal of what Dr. Pottenger has so clearly described to us.

The first bracket is divided into two sections. Certainly, I think most folks will agree that a specific allergen is responsible for most outbreaks of allergic disease. On the other hand, there are cases in which we cannot find a specific protein or allergenic cause so that it is conceivable that these two reactions may occur to produce an allergic attack without the intervention of the first or specific series of causes.

Allergic equilibrium or balanced allergic state is another term for the vagotonic predisposition which Dr. Pottenger was speaking about, and that is where I must apologize for having attempted to bring in another term that means the same thing essentially which Dr. Pottenger has discussed. The rest of the chart does not enter into the present discussion.

Of course, heredity is probably the most important predisposing factor. We may possibly have an allergically predisposed individual caused by liver insufficiency. The French have talked long about deficient gastric leucopedesis. They measure it in this way: The gastric contents usually contain a variable number of leucocytes which have passed through the stomach wall into the stomach and they quantitate these leucocytes, after the ad-

ministration of a peptone solution. They find that in asthmatics, there is often a diminished number of leucocytes in the stomach contents after stimulation caused by the ingestion of peptone solution.

That is going to be of some interest in the near future because of the recent work that has been done, first, on the use of nitrohydrochloric acid in the relief of hay fever, and second, the observation which was reported at the May meeting of the Society for the Study of Asthma, that achlorhydria often accompanies allergy.

I shall not go into further detail. I want to bring out the second bracket of my chart in confirmation of Dr. Pottenger's discussion and emphasizing the fact that there are two factors to the allergic reaction.

Dr. F. M. Pottenger, Monrovia, Calif.—I have nothing further to say. I am very glad to see Dr. Vaughan's chart.

Of course, terminology is one of the very difficult things in medicine, and it is particularly difficult when we are taking up new subjects of this kind, but it is impossible for any of us to jump right at the end of things when we begin.

I used the word "parasympathetic" in preference to vagotonia simply because I am trying to get the whole study of the vegetative nervous system on a definite basis. The vagus nerve does not include all of the parasympathetic nerves, so I think it is very much better if we speak of a person suffering from sympathicotonia and parasympathicotonia, although the words are quite long.

The thing that has interested me in asthma has been this: Why does a person become asthmatic? Why does one individual react to pollen, or to other allergens? Why does he react to stimulations of various kinds, and why does he react to various weather changes, and so forth, where another person is not bothered at all? That has been the purpose of my study more than anything else. I think we must take it into consideration with Dr. Vaughan's chart. I think he has a very splendid expression here.

We are very apt to look at all subjects, not only in medicine, but everything else, from too narrow a standpoint. It is very hard to be broad. It is very hard to get a conception of the other fellow's point of view. Medicine is made up of so many specialties today that it is almost impossible for anybody to talk on any one subject intelligently. My reason for bringing this paper before you was not in any way to oppose the idea of allergy, but simply to call attention to something more fundamental upon which your allergy is acting; and that brings up the fundamental characteristics of the individual and his particular methods of reaction. I think we must study those things.

In medicine we must go back to heredity. We have to take up the question of disposition as we have never attempted before. We are entering on the physiologic era. I think the next move is to begin this study of physiology with the instructive studies which have already been made on psychology, physiology, neurology, and the physics of the cell as they alter the patient's individual reaction. I do not know any place where it is more necessary to know this than it is in the study of the asthmatic, because the asthmatic is an individual who gives an entirely different type of reaction from other ordinary diseases in which the physiology of the individual is probably the fundamental factor.

PATHOLOGY OF ASTHMA; NONBACTERIAL ALLERGIC AND BACTERIAL TYPES BASED ON AUTOPSY MATERIAL*

By Bernhard Steinberg, M.D., and K. D. Figley, M.D., Toledo, Ohio

THE pathologic changes occurring in people affected with asthma are not well defined either in the mind of the pathologist or of the clinician. This lack of clarity is due to the questionable etiology and paucity of the postmortem material. Asthma is seldom the direct cause of death. Out of a thousand cases, Rackemann[1] reports five deaths and an autopsy on only one of them. The literature contains studies of twenty-five cases. Huber and Koessler[2] collected fifteen and presented six of their own. Lemierre, Leon-Kindberg and Levesque[3] reported one; Rackemann[1] one, and Dehner[4] two cases. All the authors, except Rackemann, classify their cases under the term of bronchial asthma. Since asthma merely means a type of dyspnea with wheezing sounds in the chest and the term bronchial refers to the involvement of the bronchi, this symptom complex was used to designate pathologic changes in what was assumed to be a distinct disease entity. Thus, Schmidt[5] considers his case that of bronchial asthma. His patient developed asthmatic attacks three weeks prior to death and the autopsy revealed a malignant growth occluding pulmonary arteries and bronchi. One of Fraenkel's cases[6] was a man of sixty-three who had rheumatism and gout for years; he had bronchial catarrh for three years and one year before death developed asthma. The autopsy revealed a dilated heart and emphysematous lungs. Tikhmeneff's[7] patient, although having asthmatic attacks for eleven years, died of empyema, pulmonary abscess, and pneumonia. Ellis,[8] from the study of his own case and those in the literature, concluded that the pathologic anatomy of bronchial asthma is not the same in all cases though in some points they closely correspond. It is apparent that it has been attempted to establish a pathologic entity for a symptom complex produced by several distinct conditions.

Meltzer's[9] association of bronchial asthma with anaphylaxis, the introduction of the allergic theory, and Walker's[10] concept of sensitization by bacterial proteins have somewhat clarified our knowledge of bronchial asthma. However, until the etiologic factor or factors are definitely determined, the employment of the term bronchial asthma, irrespective of etiologic evidence, lends confusion to an already confused subject and makes it difficult to establish a pathologic entity.

In a number of the twenty-five reported cases, the asthmatic attacks were preceded by bronchitis or sinus infections. Berkhart's[11] patient had been subject to frequent colds since childhood and the first attack of asthma followed

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a prolonged bronchitis. One of Huber and Koessler's[2] patients had a severe bronchitis for six months prior to the first attack of asthma. One of our cases had sinus infection and bronchitis prior to the appearance of asthma. It is the concensus of opinion that there is a type of asthma which is preceded by an infectious process of the sinuses, respiratory passages, or both. For this condition, we are employing the term bacterial asthma which is now in frequent use. Whether the asthmatic attacks are due to sensitization by bacterial proteins or to some other factors is irrelevant so far as the employment of the term is concerned. The pathologic anatomy of this type of asthma can be differentiated from the other type to be discussed.

In another group of the twenty-five cases, there was no evidence of any infectious process. There was usually present a familial history of asthma. If due to pollen, the attacks were more or less seasonal. If foods or animal emanations were responsible, removal of the offending factors relieved the patient. Cutaneous tests not infrequently gave positive reactions to extracts of pollen, foods, or animal emanations. This type of asthma we are indicating as nonbacterial allergic asthma.

Of the twenty-five cases reported, only eight actually died from asthma. Rackemann[1] analyzed Huber and Koessler's twenty-one cases and found only four whose deaths were due to uncomplicated asthma. The additional four cases were those of Rackemann, Lemierre, Leon-Kindberg and Levesque, and Dehner. We are adding to the literature two more cases: one of nonbacterial allergic asthma dying during an asthmatic attack and another case of bacterial asthma.

NONBACTERIAL ALLERGIC ASTHMA

Clinical History.—Female, aged sixty, married, American, was first seen by one of us (K. D. F.) at Toledo Hospital, April 23, 1927, suffering from frequent severe attacks of asthmatic dyspnea.

Family History.—One sister had asthma. Brother's child has had Fall-type of hay fever for several years.

Previous History.—Married forty years. Had given birth to two children at seventh month of gestation and neither child survived. First asthmatic attack began at her home at Archbold, Ohio, at the age of forty-two. This attack followed mowing of the lawn. Since then, asthmatic attacks have occurred the year round, but always worse and more frequent during the summer months. These attacks were often preceded by sneezing, coryza, lacrymation and burning of the eyes. Of late years, the patient noted some dyspnea on exertion, which was relieved by rest. This dyspnea occurred independently of her attacks of asthma.

Present Illness.—The asthmatic attacks began at her home the latter part of March, 1927. These attacks occurred daily and several times during twenty-four hours, and were usually worse at night.

Physical Examination.—Woman of medium build. Slight cyanosis of lips and nails. The mucous membrane of nose was pale and there was polypoid change of right middle turbinate. The sinuses were clear on transillumina-

tion; corroborated by a competent rhinologist and by roentgenogram. The chest was somewhat barrel-shaped. The heart was of normal size, the rhythm was regular but the rate persistently rapid. During attacks, there were wheezing sounds in the chest with a lengthened and labored expiratory phase. The blood pressure averaged 140/80. The electrocardiogram showed tachycardia, low amplitude of curves in all leads and a suggestion of right ventricular preponderance. Examination of the abdomen, extremities, and reflexes gave normal findings.

Blood: Hemoglobin 76 per cent; red blood cells 3,910,000; leucocytes, 8,800; polymorphonuclears 79 per cent, lymphocytes 19 per cent, eosinophiles 2 per cent. Urine: amber, acid, specific gravity 1020; trace of albumin, few white blood cells. Blood sugar 84 mg. per 100 c.c. of blood; blood nonprotein nitrogen 36 mg.; blood urea 7.8 mg. Blood calcium 9.8 mg.; blood Wassermann negative. No sputum could be obtained.

Cutaneous tests on April 25, 1927, gave mildly positive reactions to ostrich feathers, rabbit hair, sheep wool, and three tree pollens. There was a suggestive positive reaction to an intradermal injection of feather extract. On May 7, 1927, other scratch skin tests gave mildly positive reactions to numerous tree, grass, and weed pollens.

Treatment and Course.—The patient was under observation in the hospital from April 23 to May 11, 1927. During this time she had repeated asthmatic attacks which were relieved by small doses of adrenalin. At no time was there coughing or expectoration either preceding or following the asthmatic attacks. About a week before her death, there occurred several days of very high winds, during which time the patient was worse—the asthmatic attacks being almost continuous. Pollen plates in the window of the patient's room showed the presence of enormous amounts of tree and grass pollens. After three days and nights of especially severe asthmatic seizures, the patient died. Death was apparently due to respiratory failure as the heart remained regular and the systolic blood pressure was maintained at a level of 130 up to death.

Clinical Diagnosis.—Nonbacterial allergic asthma, probably due to pollen.

Points in the case report that point to an allergic basis for the asthmatic attacks: The onset of the original attack in summer following cutting grass; the attacks more frequent and worse in summer; the attacks formerly preceded and accompanied by symptoms of hay fever; history of allergic manifestations in other members of the family; allergic appearance of nasal mucosa; positive cutaneous tests to numerous tree, grass, and weed pollens as well as a few animal emanations; extremely severe asthmatic attacks prior to death coincident with presence of large amounts of tree and grass pollens in the air.

PATHOLOGIC REPORT

Macroscopic Description.—The body is that of a well developed and moderately well nourished, white adult woman. The shape of the chest is suggestive of a half barrel. The abdomen is protuberant. There is slight edema of

the lower extremities and cyanosis under finger nails. The liver extends 5.5 cm. below the costal margin. The heart weighs 275 gm., is brown in color and shows a decrease in the subepicardial fat. The left ventricular wall measures 14 mm., the right ventricular wall 8 mm., the left auricular wall 3 mm. and the right auricular wall 1 mm. The right ventricular wall shows penetration of yellow streaks from the subepicardial fat into the musculature. The right lung weighs 300 gm., and the left 240 gm. The lungs contain large areas of bulbous emphysema and are reddish-yellow in color. The cut surface is dry, spongy, and red-yellow. The trachea and large bronchi have a red mucosa which is covered with a red, slimy material. The bronchioles, the small and medium sized bronchi contain white, firm plugs, which obliterate the lumen completely in the greater number of tubes. These plugs cannot be dislodged even by firm pressure. The spleen weighs 135 gm.; the cut surface is purple-red and the knife scrapes away very little of the pulp. The connective tissue is increased. The liver weighs 1230 gm. The edges are sharp. At the junction of the superior and anterior surfaces are two ridges 4 mm. in width and 3 cm. in length. Both kidneys weigh 270 gm. The capsule strips without difficulty leaving a smooth, nongranular surface containing fetal lobulations. The left kidney, in the cortex and medulla of the upper pole, contains an encapsulated, grey-yellow, elevated, soft mass, 4 cm. in diameter. The brain shows moderate edema. The other organs do not show any significant changes.

Microscopic Description.—The heart shows, in the right ventricular wall, separation of muscle bundles by "signet-ring" cells. The muscle cells contain a moderate amount of bipolar brown pigment. The blood vessels are congested. The spleen contains thickened blood vessels. The follicles are smaller than normal and contain small areas of a homogeneous pink staining (eosin-stained) amyloid. The sinuses are distended with blood. The mass in the upper pole of the left kidney consists of tubules lined by cuboidal epithelium. The epithelium is nowhere outside the basement membrane. The tubules are confined by a connective tissue capsule. The lungs show the greater number of the alveoli distended and intercommunicating through broken-down septa. The alveolar lumina are clear. The interalveolar tissue contains dilated and congested capillaries and blood vessels. The bronchioles, small and medium sized bronchi, are dilated; the lumina are entirely or partly occluded by mucus which contains desquamated epithelial and few mononuclear cells, some of which are eosinophilic. The mucous material is adherent in many places to the epithelium. The lining cells are everywhere intact. The basement membrane is hyalinized in the greater number of bronchi and bronchioles. The subepithelial tissue is edematous and is infiltrated by a large number of mononuclear cells, many of which are eosinophilic. The muscle layer is markedly thickened. The mucous glands show absence of nuclei, obliteration of cell outline and a hypersecretion of mucus. The muscle layer and the glands are infiltrated by mononuclear cells many of which are eosinophiles.

SUMMARY OF THE PATHOLOGIC FINDINGS IN THE LUNGS

Complete or partial obliteration by mucous plugs of the lumina of most of the bronchioles, small and medium sized bronchi; hyperplasia, hypertrophy and hypersecretory activity of the mucous glands; hypertrophy of the muscle layer; edema and cellular infiltration of all the coats; a large number of eosinophiles in the cellular exudate; emphysema.

Fig. 1.—***Nonbacterial allergic asthma.*** Cross-section of bronchi, small and medium size, and lung tissue. *a*, Lumen of bronchus completely filled by mucous material; *b*, muscle layer shows hypertrophy; *c*, the mucous glands are hyperplastic, hypertrophied and show hypersecretory activity; *d*, lung tissue showing emphysematous areas. (x10)

Fig. 2.—***Nonbacterial allergic asthma.*** Cross-section of bronchus in Fig. 1 under higher magnification. *a*, Lumen of bronchus completely filled with mucoid material and cells, the lumen is distended and tortuous; *b*, hypertrophic muscle layer; *c*, hyperplastic, hypertrophic and hypersecreting mucous glands; *d*, cartilage. (x30)

Fig. 3.—*Nonbacterial allergic asthma.* Cross-section of bronchus of 2 mm. inside diameter. *a*, Lumen of bronchus completely filled with spirally arranged mucus; *b*, hypertrophied circular muscle bundles; *c*, mucous glands showing hypersecretory activity, hyperplasia and hypertrophy. (x45)

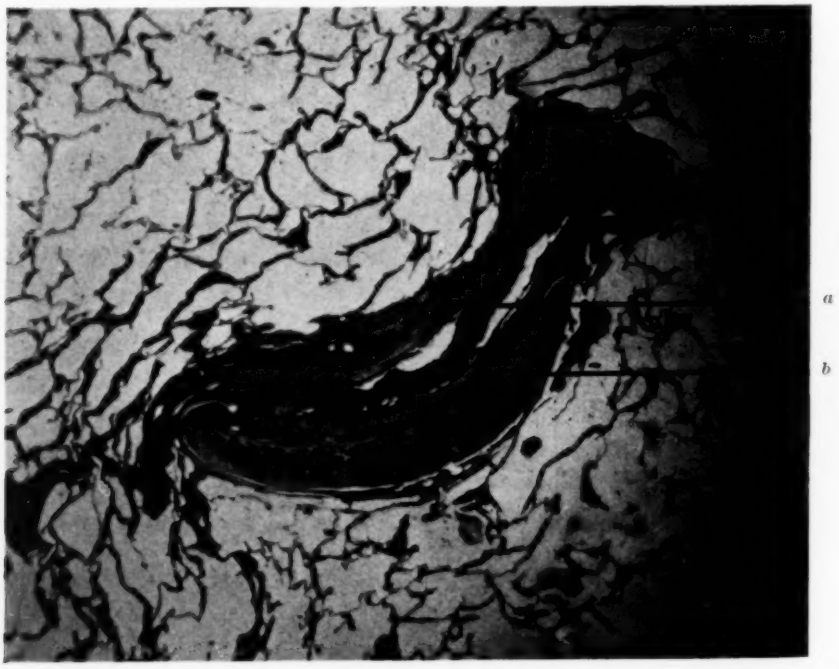

Fig. 4.—*Nonbacterial allergic asthma.* Cross-section of bronchus, 1 mm. inside diameter. *a*, Greatly hypertrophic muscle layer; *b*, lumen almost completely filled with mucous material (x45)

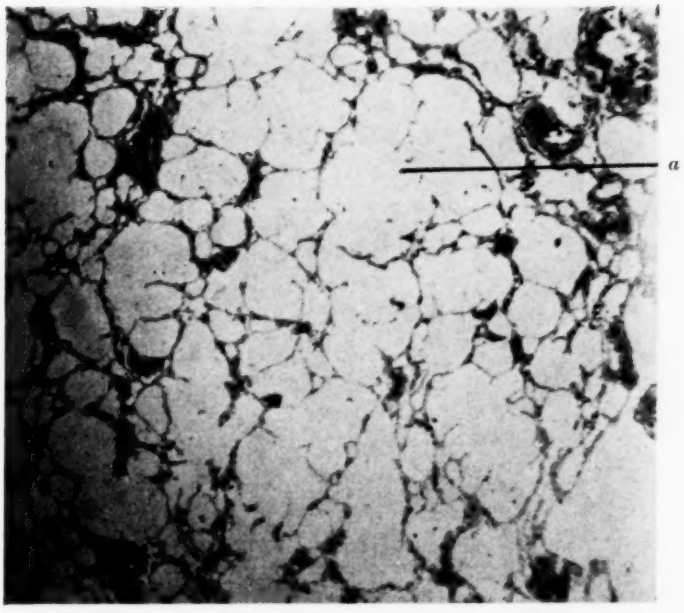

Fig. 5.—*Nonbacterial allergic asthma.* Cross-section of lung showing emphysema. *a*, the alveoli are distended, the interalveolar walls are broken through and several alveoli intercommunicate. (x45)

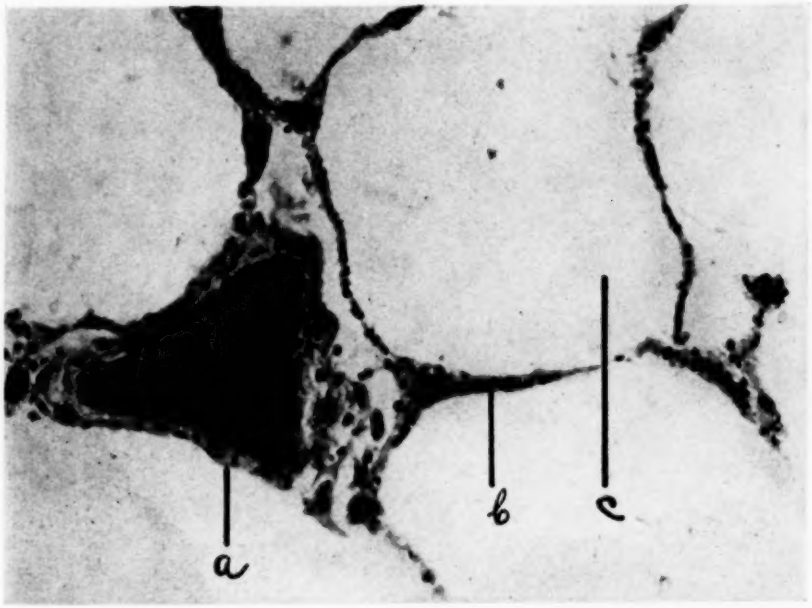

Fig. 6.—*Nonbacterial allergic asthma.* Cross-section of lung with emphysema. An area from Fig. 5 under higher magnification. *a*, Blood vessel is distended and filled with blood; *b*, distended capillaries filled with blood; *c*, dilated alveolus.

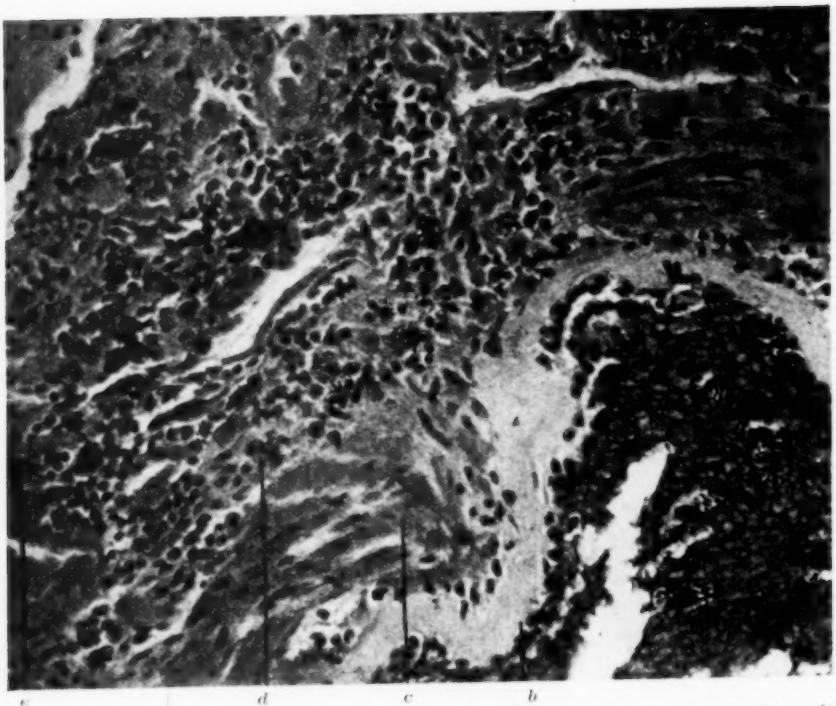

Fig. 7.—*Nonbacterial allergic asthma.* Cross-section of a part of bronchus with an inside diameter of 3 mm. *a*, Lumen of bronchus filled with mucoid material which contains desquamated epithelial cells and eosinophiles; the mucus is firmly adherent to the lining epithelium; *b*, hyalinized subepithelial tissue; *c*, hypertrophic muscle layer diffusely infiltrated by mononuclear cells, many of which are eosinophilic; *d*, eosinophile; *e*, lymphatic filled with coal pigment. (x500)

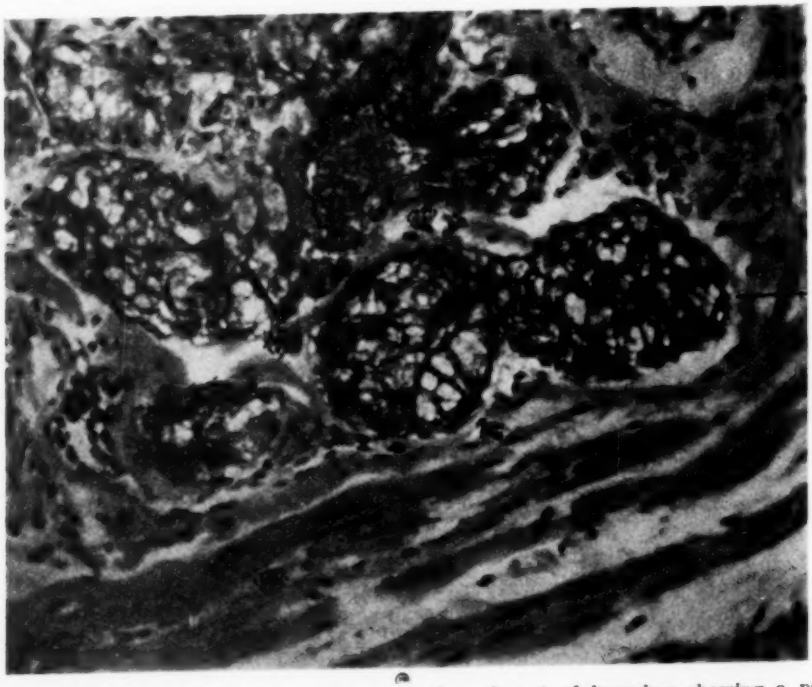

Fig. 8.—*Nonbacterial allergic asthma.* Section of part of bronchus showing a part of the muscle layer and the mucous glands. *a*, The mucous glands show hypertrophy, loss of nuclei and cytoplasm and a large amount of mucous secretion. There are many mononuclear cells infiltrating the glands, some of these cells are eosinophiles. (x500)

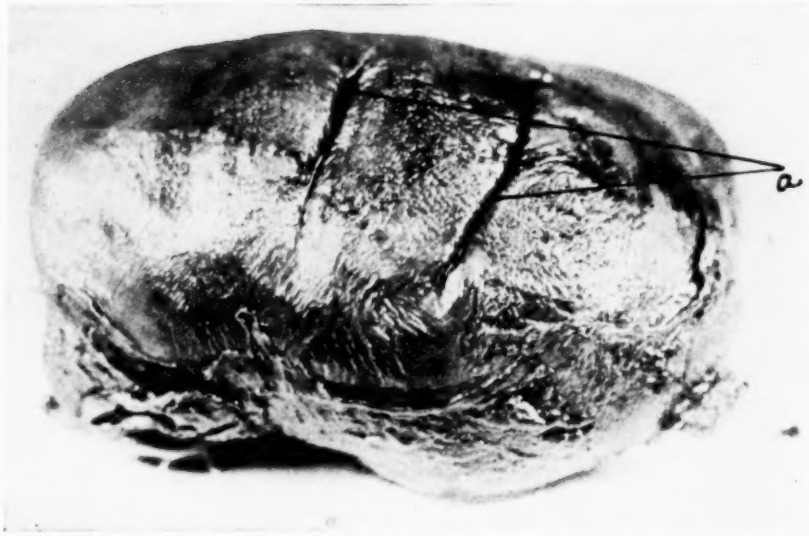

Fig. 9.—*Nonbacterial allergic asthma.* Gross photograph of the liver. *a*, Two notches on the superior surface due to pressure of diaphragm as a result of emphysematous lungs.

Pathologic Diagnosis.—Chronic emphysema of lungs, marked; chronic obstructive bronchitis; brown atrophy of the heart; fat infiltration of the heart; tubular adenoma of the left kidney; edema of the brain.

BACTERIAL ASTHMA

Clinical History.—Mrs. E. A. U., aged sixty-one, married, Swiss-American, was first seen by one of us (K. D. F.) in July, 1922, suffering from severe paroxysms of coughing and asthmatic dyspnea.

Family History.—Husband has arrested pulmonary tuberculosis. Three daughters are living and well. There is no history of allergic manifestations in the family.

Previous Medical History.—Typhoid fever at the age of twelve with complete recovery. Married at the age of twenty-five. Mother of three healthy, living children. Always well since attack of typhoid until present illness.

Present Illness.—In May, 1922, patient had a severe attack of so-called "influenza." This was followed by paroxysms of coughing which were usually unproductive and severe enough to provoke vomiting. Eventually, these coughing spells led to the asthmatic type of dyspnea. The dyspnea and cough became progressively worse. On August 5, 1922, patient was first admitted to Toledo Hospital.

Physical Examination.—Woman of fifty-five with evident respiratory distress, coughing frequently and leaning forward with each paroxysm of coughing. Some cyanosis of face and lips. Nails cyanotic. Nasal mucosa showed evidence of a chronic inflammatory process and there were polypi in right upper nasal fossa. Frontal sinuses and the antra were clear on transillumination. This was corroborated by roentgenogram and by a competent rhinologist. Chest showed physical signs of emphysema. Throughout both lungs,

there were numerous dry and moist sibilant râles of all degrees of intensity. Breathing was of the asthmatic type with a lengthened and difficult expiratory phase. The heart was impossible to outline on physical examination but the roentgenogram showed slight enlargement to the left. The rate was somewhat increased but the rhythm was regular. Blood pressure was 140 systolic, 80 diastolic. The liver edge was palpable two fingers' breadth below the costal margin; there were no other abnormal abdominal findings. Examination of reflexes, glands, extremities gave normal findings.

Blood: Hemoglobin 80 per cent; red blood count 4,200,000; white blood count 10,000; polymorphonuclears 75 per cent, lymphocytes 20 per cent, eosinophiles 5 per cent. Urine: amber, specific gravity 1021, acid. Wassermann negative. Cutaneous tests: All negative to various foods, pollens, animal emanations, house dust, etc.

Treatment and Course.—During this admission, a large polypus containing green, muco-pus was removed from the right upper nasal fossa by Dr. E. G. Galbraith, who expressed the opinion that it originated from chronic ethmoid infection. Under rest and sedatives, the asthmatic dyspnea gradually subsided, especially after the expectoration of large amounts of thick, greenish sputum was well established.

Following this admission, the patient was seen at home several times during the late fall of 1922. She had severe attacks of asthmatic dyspnea and paroxysmal cough. These attacks were always made worse by the slightest exertion and were relieved by the raising of thick, green, muco-purulent sputum. In February, 1923, the patient developed broncho-pneumonia and was admitted to Toledo Hospital. There was again much asthmatic dyspnea with raising of thick sputum. During this admission, an electrocardiogram showed some myocardial impairment with numerous extrasystoles. On December 11, 1924, the patient was again admitted to Toledo Hospital, having had several attacks of asthmatic dyspnea at her home, since her last admission. These attacks usually followed "taking cold" and were relieved when expectoration was freely accomplished. During this admission, Dr. Galbraith irrigated the left maxillary sinus with prompt relief from the distressing cough and dyspnea. Roentgenogram of the sinuses showed abnormal changes in the ethmoids and in the left maxillary antrum. In March, 1927, following the usual succession of asthmatic attacks at intervals of several weeks to months, the patient was again admitted to Toledo Hospital. This time, the dyspnea was relieved more quickly by ephedrin. The roentgenogram showed no change in the heart shadow as compared with previous examinations. The antra were clear. Urine and blood showed normal findings. Blood urea nitrogen was 15 mg.; CO_2 combining power 68. Sputum culture showed a pneumococcus type IV. Wassermann was again negative and repeated cutaneous protein tests were negative. On February 15, 1928, the patient was again seen at her home with the complaint of cough and severe headache. She stated she had not felt well for three days and thought she had "taken cold." She became unconscious shortly after and was removed to Toledo Hospital where she died on February 23, 1928. During her stay in the hospital, she was almost com-

pletely anuric, and had intractable vomiting, and several convulsions, which started with twitchings of the left arm and leg. Leucocytes 25,000 with 87 per cent polymorphonuclears. Blood nonprotein nitrogen 120 mg.; urea nitrogen 75 mg.; creatinin 4 mg. Spinal puncture returned a normal fluid under normal pressure. Urine showed much albumin, granular and epithelial casts, numerous white blood cells and red blood cells.

Clinical Diagnosis.—Bacterial asthma (asthmatic bronchitis); death due to bacteremia from sinus or bronchial infection; acute nephritis.

PATHOLOGIC REPORT

Macroscopic Description.—The body is that of a well developed, well nourished, white, adult woman. The nose shows excoriation and deviation of the septum to the left. There is pyorrhea alveolaris. There is moderate edema of the extremities and cyanosis of finger nails. The upper lobe of the right lung is adherent by firm fibrous adhesions anteriorly and posteriorly. The lungs fill completely both pleural cavities. The liver extends for 4 cm. below the costal margin. The heart weighs 380 gm. There are small subepicardial hemorrhages. The right lung weighs 630 gm.; the left lung 435 gm. There is moderate emphysema, more marked in the middle and lower right lobes. In the emphysematous areas, the lung is crepitant, elsewhere it is rubbery in consistency. A creamy pus is expressed on pressure from the cut surface. The trachea, the large and middle sized bronchi show a red mucosa covered by yellow purulent material. The smaller bronchi are filled with yellow pus. The pulmonary arteries show occasional elevated areas of intimal thickening. The lymph nodes are large and anthracotic. The liver weighs 1130 gm. The edges are round. The cut surface shows deep red central zones surrounding the central veins. The combined weight of both kidneys is 410 gm. The cortex measures 8 mm. The striations are parallel and regular. The glomeruli are red. The brain shows diffuse hemorrhages in the right cerebral cortex. The sphenoid and ethmoid sinuses are filled with a yellow-grey material. The posterior nares contain yellow pus. The mastoid cells and middle ears show no abnormal changes.

Microscopic Description.—Heart shows diffuse subepicardial hemorrhages. The capillaries are distended and congested. There is some fragmentation of myocardial cells and patchy replacement of muscle by fibrous connective tissue. The splenic capsule is increased in thickness. There is a greater than normal amount of fibrous connective tissue. The sinuses are distended with blood. Liver shows necrosis of central zones with a diffuse infiltration of the necrotic areas by red blood cells. The kidney shows replacement of cortical areas by connective tissue with presence of few lymphoid cells. Some glomeruli are completely fibrosed. The subcapsular space in a number of the glomeruli contains albuminous material. The capillary tufts are distended with blood and show an increased cellularity. The tubules, especially the proximal convoluted, contain hyaline casts, albuminous material and red blood cells. The brain shows an infiltration of the vessel walls by polymorphonuclears and mononuclears. In places, the vessel walls are ruptured and red

blood cells are seen in the break and in the surrounding brain tissue. The cortex of the brain shows in places pycnosis and caryorrhexis of nuclei and destruction of cell cytoplasm. An occasional blood vessel shows an embolus consisting of bacterial masses and cells. Lungs show large patches in which the alveoli are obliterated; many of these areas consist of connective tissue. The bronchioles and the bronchi of the smallest caliber, between 0.5 and 1 mm. inside diameter, show within the lumina a cellular exudate consisting of broken and intact polymorphonuclears and mononuclears. The lining cells are absent in many places; in other places, there is metaplasia from columnar to squamous epithelium. The walls are diffusely infiltrated by similar cells. There is only an infrequent eosinophile. An occasional small bronchus shows obliteration of the lumen by connective tissue. The muscle layer of the bronchioles and of the small bronchi is moderately hypertrophied. The mucous glands show no change except for a moderate infiltration by mononuclear and polymorphonuclear cells. An occasional cartilage shows a bone marrow reaction. The medium and the larger sized bronchi show within the lumina only a small amount of a cellular exudate but the walls contain foci as well as a moderate infiltration of polymorphonuclears and mononuclears.

Summary of the Pathologic Findings in the Lungs.—Atelectasis; cellular exudate filling the lumina of the bronchioles and small bronchi; destruction of the lining cells of the mucosa; diffuse infiltration of the walls by polymorphonuclears and mononuclears with an infrequent eosinophile; intact mucous glands; a moderate hypertrophy of the muscle layer; occasional marrow reaction in cartilage surrounding bronchi; fibrous connective tissue replacement of the lumina of some of the small sized bronchi.

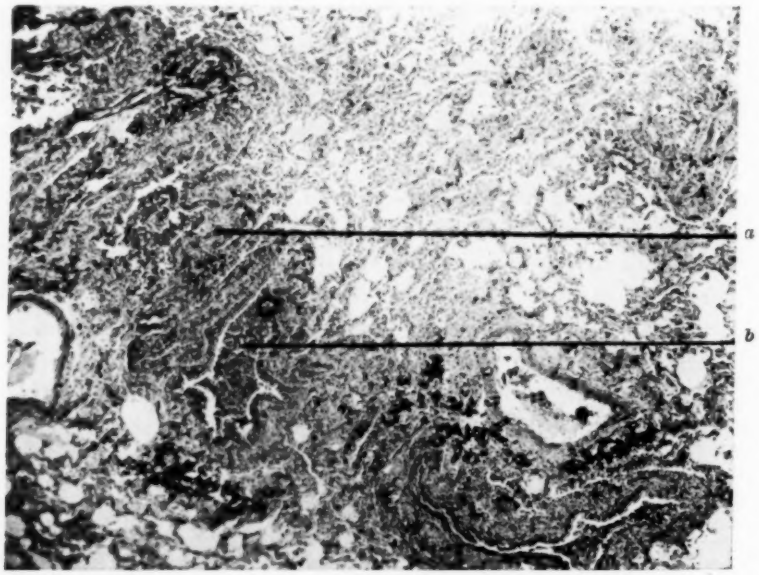

Fig. 10.—*Bacterial asthma.* Cross-section of lung and bronchi, 1 mm. or less, inside diameter. The bronchi are distended and filled with an exudate. *a*, Atelectatic lung tissue; *b*, bronchus filled with a cellular exudate. (x30)

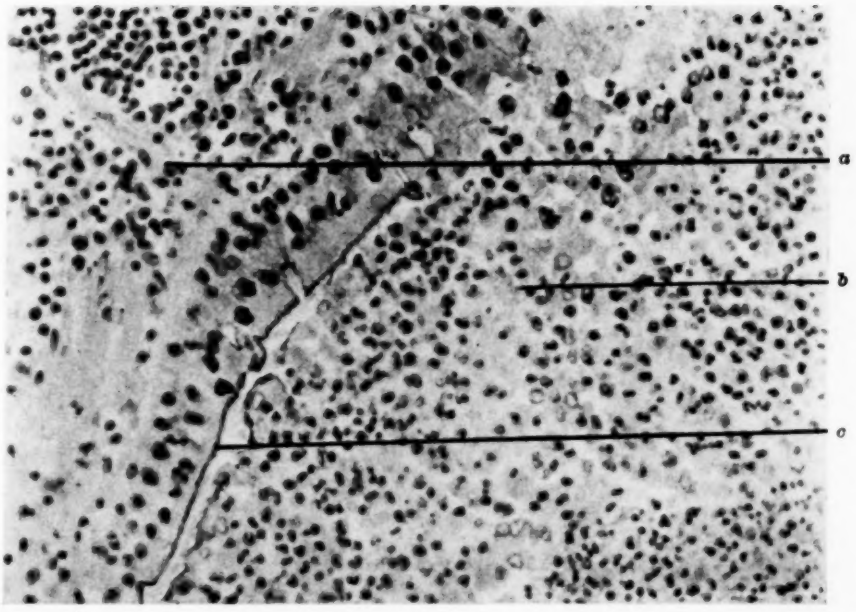

Fig. 11.—*Bacterial asthma.* Section of part of bronchus taken from the area marked with circle in Fig. 10. *a*, Muscle layer infiltrated by broken and intact polymorphonuclears and mononuclears, the muscle bundles are moderately hypertrophic; *b*, lumen of bronchus filled by a cellular exudate consisting of broken and intact polymorphonuclears and mononuclears; this field does not show a single eosinophile; *c*, lining epithelial cells. (x500)

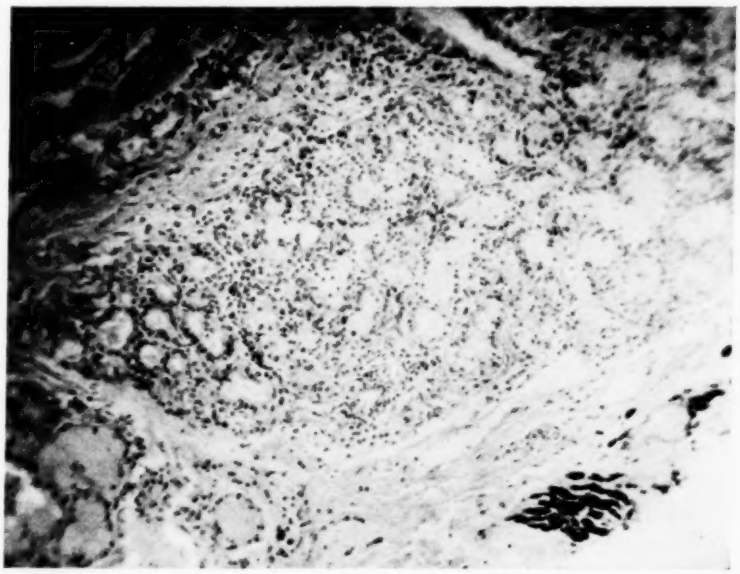

Fig. 12.—*Bacterial asthma.* Section of part of wall of a bronchus, 2 mm. inside diameter, showing mucous glands which are diffusely infiltrated by cells. (x60)

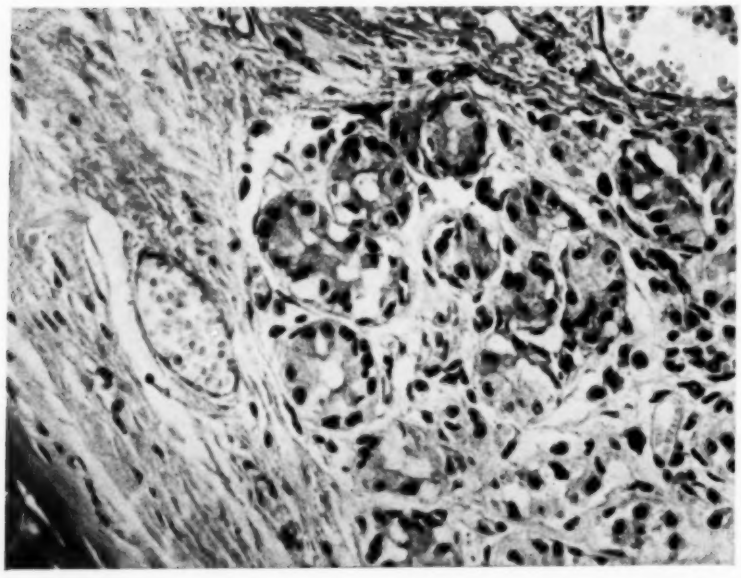

Fig. 13.—*Bacterial asthma.* Section of part of bronchial wall showing several mucous acini. The nuclei are preserved, the cytoplasm is intact, and there is absence of mucous secretion.

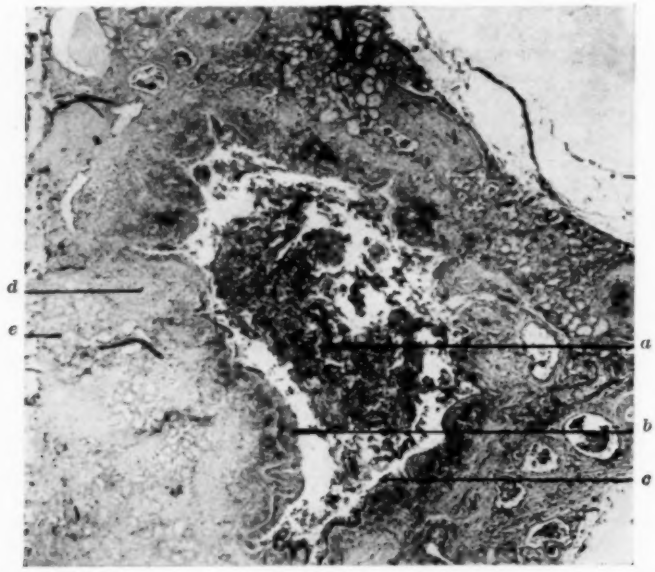

Fig. 14.—*Bacterial asthma.* Cross-section of bronchus with an inside diameter of 2 mm. *a*, Lumen filled with a cellular exudate; *b*, apparent metaplasia of lining epithelium; *c*, columnar epithelium on the opposite side of the transitional epithelium; *d*, hypertrophic muscle layer; *e*, intact mucous glands. (x60)

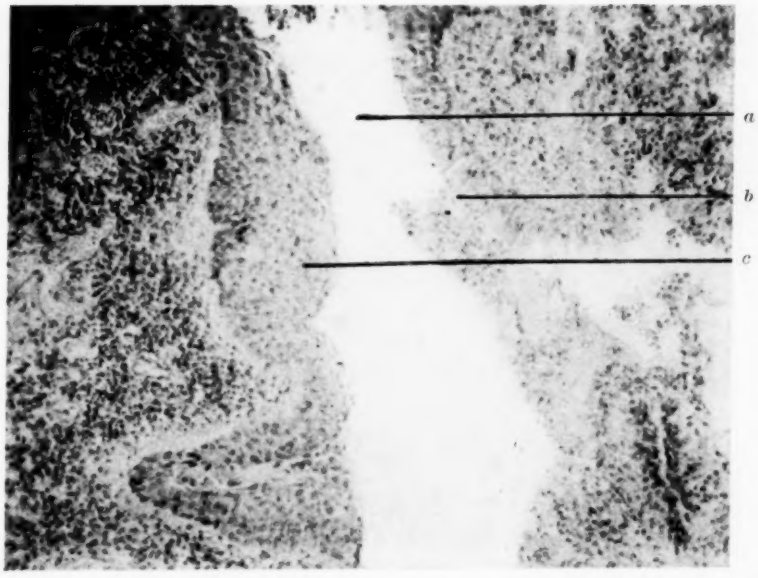

Fig. 15.—*Bacterial asthma.* Section of lining mucosal cells of bronchus in Fig. 14. *a*, Lumen of bronchus; *b*, columnar epithelium; *c*, transitional epithelium. (x300)

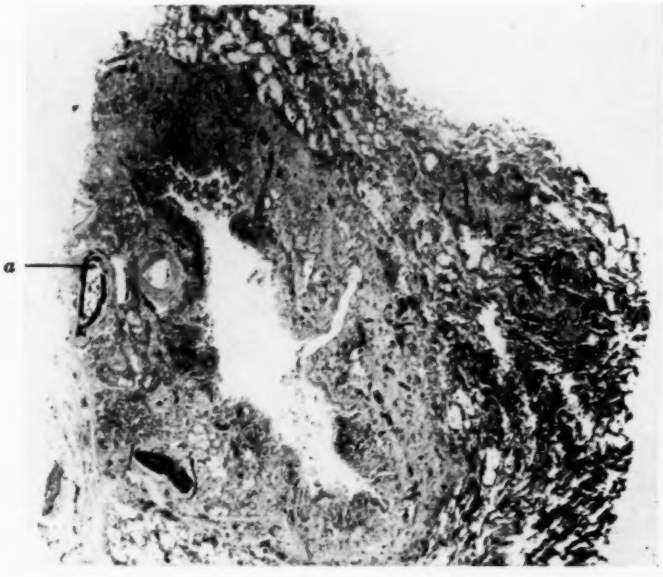

Fig. 16.—*Bacterial asthma.* Section of bronchus. *a*, Cartilage showing bone marrow reactions. (x100)

Pathologic Diagnosis.—Chronic with superimposed acute purulent bronchitis; atelectasis of lung; subepicardial hemorrhages; fibrosis of myocardium, slight; chronic with superimposed acute glomerulonephritis; hemorrhagic necrosis of liver; acute arteritis of vessels of brain with encephalomalacia, early.

Fig. 17.—*Bacterial asthma.* Section of lung showing atelectatic areas. *a*, Area of atelectasis. (x10)

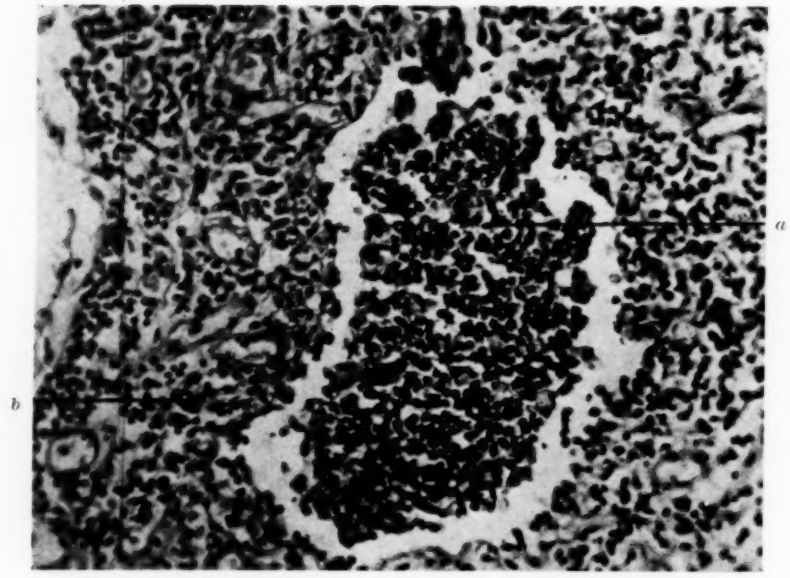

Fig. 18.—*Bacterial asthma.* Section of bronchus, 0.4 mm. inside diameter. *a*, Lumen shows a cellular exudate consisting of broken and intact polymorphonuclears and mononuclears; *b*, the bronchial wall is diffusely infiltrated by mononuclears and polymorphonuclears; the capillaries are distended. (x300)

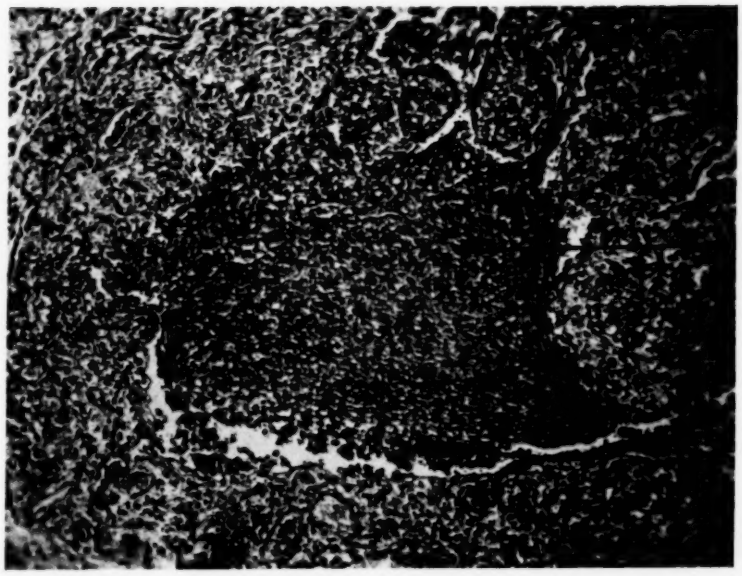

Fig. 19.—*Bacterial asthma.* Section of small bronchus. *a*, Remnant of lining epithelium; *b*, lumen completely obliterated by fibrous connective tissue which contains many mononuclear cells. (x60)

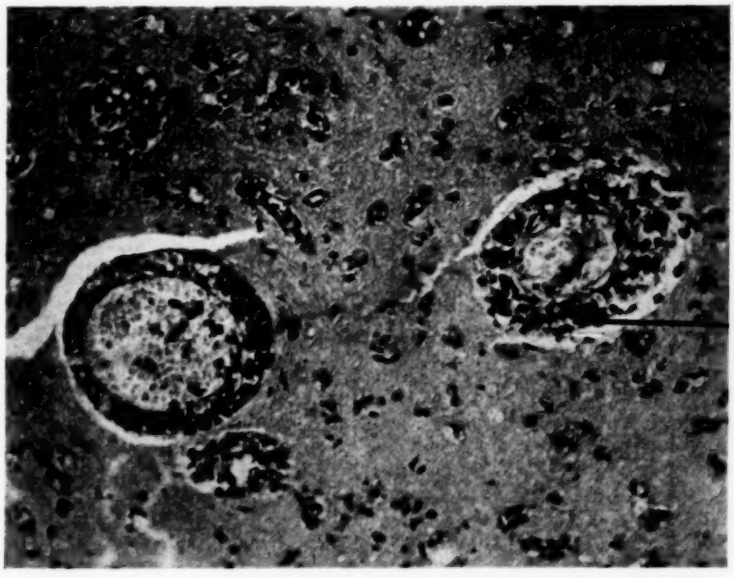

Fig. 20.—*Bacterial asthma.* Section of brain showing blood vessels. *a*, Blood vessel showing a diffuse infiltration of the wall by polymorphonuclears and mononuclears. (x300)

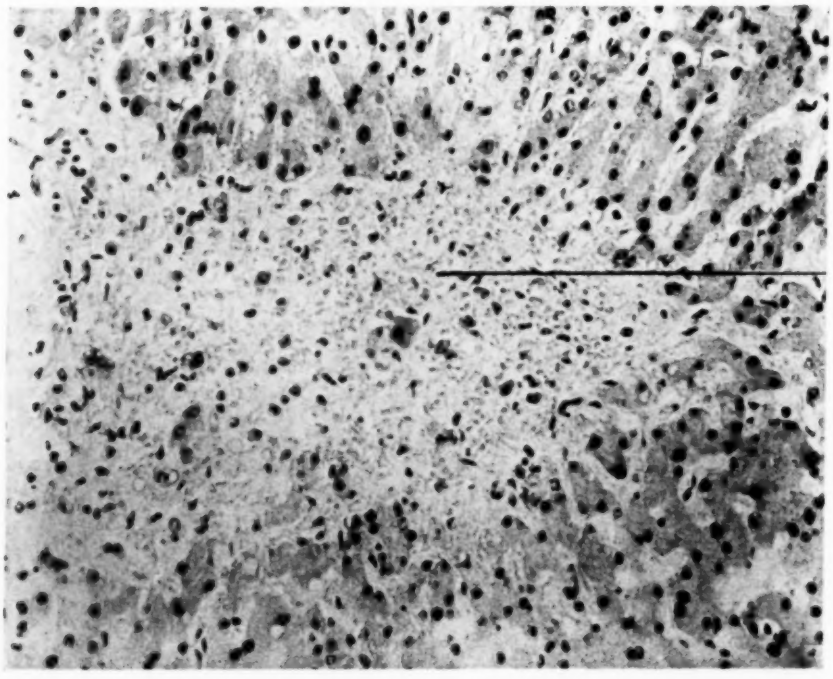

Fig. 21.—*Bacterial asthma.* Section of liver. *a*, Central zone of necrosis showing destruction of nuclei and cell cytoplasm and presence of red blood cells. (x500)

PATHOLOGIC CHANGES IN NONBACTERIAL ALLERGIC AND BACTERIAL ASTHMA

Nonbacterial Allergic Asthma	*Bacterial Asthma*
1. Marked emphysema.	1. Slight emphysema.
2. No atelectasis.	2. Moderate atelectasis.
3. Lumen of large, medium and small bronchi and bronchioles partly or entirely occluded.	3. Lumen of small bronchi and bronchioles partly or completely occluded.
4. Material in the bronchial lumina mainly mucoid which adheres to lining cells.	4. Material in the bronchial lumina mostly cellular and it does not adhere to lining cells.
5. Little or no destruction of the lining bronchial epithelium.	5. Moderate to marked destruction of the lining bronchial epithelium.
6. Marked hypertrophy of the bronchial musculature.	6. Moderate hypertrophy of the bronchial epithelium.
7. A large number of eosinophiles in the cellular exudate within the lumen and in the bronchial wall.	7. Few eosinophiles in the cellular exudate within the lumen and in the bronchial wall.
8. Hypertrophy, hyperplasia and hypersecretory activity of the mucous glands.	8. Hyperplasia of the mucous glands but little secretory activity.

DISCUSSION

Patients affected by nonbacterial allergic asthma over a long period of time, not infrequently show a superimposed bacterial process. Such an infection confuses the pathologic picture of the original condition by altering

or adding new abnormal changes. Our case, both clinically and pathologically, shows absence of any secondary process. We are, therefore, dealing with an uncomplicated allergic asthma which eventually produced death of the patient. By the same token, the morbid anatomy is presumably the result of allergic asthma.

The anatomic changes in allergic asthma are apparently entirely restricted to the lungs. There is emphysema. The cause of the emphysema is still disputed, and the solution of this problem may advance greatly our knowledge of the etiology of asthma. It is generally accepted that emphysema is the result of occlusion of bronchial lumina. Although foreign material in form of mucous plugs or cellular exudates is consistently found within the bronchial tubes, many students of the subject hypothecate that the closure of the tubes is due to repeated spasmodic contractions of the bronchial musculature. There is a great deal of indirect experimental evidence that substantiates this theory. Hoover pointed out that stenosis of the bronchial tubes may be due to an evanescent edema of the bronchial wall. The bronchi show marked changes. The lumina of all except the largest bronchi are completely or partly occluded by mucous plugs. The failure of the patient to raise any bronchial secretion may be explained by the adhesion of the mucus to the bronchial epithelium. It is probable that when the bronchial lumen is completely filled and the further secretion of the glands is dammed, degenerative changes that are found in the mucous glands result. Whether the glandular hypersecretory activity is due to irritation from the cellular infiltration, or nervous stimulation, or is a result of muscular contractions remains a problem to be solved. The hypertrophy of the muscle layer has been a constant finding. In our case it is apparent. It has been assumed, as a result of indirect experimental evidence, that the muscular hypertrophy is due to spasmodic contractions. However, the bronchi may be contracting to expel the foreign material in the lumen and the hypertrophy is merely a result of increased effort. We have an analogy in the heart which hypertrophies to compensate for an additional load.

The bronchial wall shows edema and cellular infiltration. Many of the cells are eosinophilic. The cause of the presence of the cells and especially of the eosinophiles has been the subject of much discussion. Huber and Koessler review extensively the underlying basis for this cellular phenomenon and they conclude with Schlecht[12] that the eosinophilia is probably a protective reaction on the part of the body against decomposition protein products that are responsible for the allergic condition.

The pathologic changes in our case of bacterial asthma differ from those in the nonbacterial allergic asthma. The lungs in the case of the bacterial asthma show evidences of a chronic bronchitis with a superimposed acute bronchitis. The diffuse infiltration of the bronchial walls with loss of epithelial structure, the presence of bacterial emboli in the vessels of the brain, the acute nephritis, and the central hemorrhagic necrosis of the liver, point to the entrance of bacteria into the blood stream. It may be assumed that in previous attacks of bronchitis a similar absorption of smaller amounts of

bacteria or their products occurred. Thus, bacterial sensitization, if such a phenomenon occurs, can be easily conceived in this case.

SUMMARY

The clinical histories and the morbid anatomy of two cases of asthma are presented. One case is of an uncomplicated nonbacterial allergic asthma dying during a paroxysm; the other is that of a bacterial asthma. The pathologic changes of the nonbacterial allergic type are differentiated from those of bacterial asthma.

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DISCUSSION

Dr. Harry L. Huber, Chicago, Ill.—First, I want to congratulate Dr. Steinberg on the patience to take the time to study out these things, as I know, from the work I have done, how long it has taken him to do all this work. All these slides look very familiar to me.

I have another case to report which demonstrates one thing that we have not been able to find in other cases. Burkhardt reported finding a small ulcer in one of the bronchi. In explaining the bacterial type of asthma, or the asthma due to bronchitis, we have often wondered if an exhaustive search were made if we would be able to find some ulceration where it was evident that toxic materials were being absorbed. In this patient I am now working on, this ulceration is very clearly demonstrated. This was a woman physician in Chicago who had had asthma and had negative skin tests. She administered morphine herself and died following an overdose. The autopsy was done and in several different parts of the lung very definite minute bronchial ulcers were found. Although we made an exhaustive study of other cases reported we were not able to find ulcers. The presence of eosinophiles we have always thought was more indicative of the allergic type of asthma.

The mucous glands shown here are large. One point I wish to emphasize is the importance of the ampullae of gland ducts. These ampullae are shown to increase the thickness of the wall, or rather to decrease the size of the lumen, and they are probably responsible for the adherence of the mucus in the bronchi. The mucous glands secrete a very sticky mucus which pours into the lumen for a time, then as the bronchi contract, the muscle bands, being inside the mucous glands, pinch down on the ducts. The gland continues to secrete and large bags of mucus accumulate outside the muscle layer. This pushes against the mucous membrane and decreases the size of the lumen. The administration of adrenalin in these patients will very frequently, when relief begins to come, cause copious discharge of mucus. It is supposed these accumulations of mucus are being expelled at this time, and as these ampulla decrease in size, the size of the bronchus increases, and breathing is more easily done.

To distinguish between the allergic and the bacterial causes of asthma, I think it will be necessary to have a little more work done as it may be that the bacterial type will also prove to be allergic.

At one of the recent meetings in Washington it was suggested that arthritis and a number of other diseases that are now considered as infectious diseases, may be due to allergy. No doubt more extensive studies are now going to be made to link up a lot of the unexplained things which, if we have a clear understanding of allergy, may help us a great deal.

Dr. Milton B. Cohen, Cleveland, Ohio.—Recently I had the good fortune to observe one of these cases at autopsy. The patient was a woman about thirty-seven or thirty-eight, who had a moderately developed mitral stenosis which was known to have existed for a number of years before she developed chronic bronchial asthma. This woman had been studied by cardiologists as well as allergists, and it was the opinion of every one that the asthma was a true asthma, and had nothing to do with cardiac pathology. At no time had she had indications of decompensation. The heart disease was extraneous as far as asthma was concerned.

This woman was a patient who was not skin sensitive to any materials to which we tested her, but whose attacks could be very well controlled by environmental change.

We have at the city hospital at Cleveland, two particle-free rooms. When I say "particle-free," I mean we have ninety-nine per cent plus particle-free air. A residence of ten days in this room afforded this patient relief and she required no epinephrin and had no attacks, whereas previously she had attacks every day. She had gone home from the hospital feeling quite well and had been home about a week and was suddenly seized with a severe attack. She was brought into the hospital and within twenty hours died of respiratory failure, simply choked to death in spite of all the epinephrin and everything else that could be injected into her, or everything that we thought of doing. At no time did she have any evidences of cardiac failure.

At autopsy, the lungs showed a picture quite like the first case that Dr. Steinberg described, except that one pathologist said the bronchial muscle looked thicker, another said it wasn't particularly thick but showed a mild bronchiolitis; but in the gross the moderate-sized bronchi were full of sticky mucoid discharge which could be pulled out, and came off more or less as a cast of the smaller bronchi.

There are one or two points of interest about bacterial asthma which I just picked up recently. Dr. Wherry in Cincinnati, who is, in my judgment, at least, one of the best bacteriologists in the country, has been studying many of these cases very intensively. It was surprising to me how many different organisms which could be got out of nasal or bronchial secretions were overlooked by bacteriologic methods. It was surprising he did not find some organisms which other men have reported to be present. However, he has been able to demonstrate by the use of fifteen or twenty of these antigens, autogenously prepared, definite tuberculin-like reactions in many cases, and has been able in quite a number to produce negative skin tests after rather prolonged courses of injections, not just one negative skin test, because we know these things vary, but skin tests remaining negative over considerable periods of time. He feels he is getting very nice results in such cases studied bacteriologically, as he studied them.

I noticed in the chart a reaction to tuna fish. Recently I made a survey of some hundred proteins that you buy on the market to find out how many had nonspecific protein split products. One particular sample of tuna fish gave us a beautiful reaction after dialysis. What we did was to put this tuna fish in solution and dialyze against the same solution, and the tuna fish gave a reaction which we took to be due to histamine or some similar substance.

It wasn't worked out any farther than that.

Dr. Ray W. Matson, Portland, Oregon.—We have been interested in the doctor's talk on pathology, in the finding of the eosinophilia. In a certain group of cases we have worked out in Portland, Oregon, we have found quite a series of sinuses. One of the men there, Dr. Kistner, has not done as Dr. Sewall has done in San Francisco. The radical sinus opera-

tion gives us some very valuable material. The finding of eosinophilia was also common in these sinus cases. Unfortunately, the bronchial asthma which was generally present in these cases was complicated by an infection, chronic sinusitis. The history, however, was clear in each case as to whether there had been an allergic history. The allergy had been worked out carefully by the cutaneous tests. The pathology in these chronic sinus cases was a hyperplasia of the columnar and squamous epithelium with often a mucous hyperplasia consisting sometimes of actual goblet cell formation. There was an edema of the submucous tissue, often extreme infiltration of cells consisting first of all of numbers of plasma cells. The next important cell was the eosinophile which sometimes infiltrated so quickly the whole field was pink with them. There were other types of cells in smaller numbers including the ordinary polymorphonuclear. Unfortunately, our figures do not indicate clearly the history of allergy or the history of nonallergy. The eosinophilia as reported by some workers is present in allergy and absent in the nonallergic cases.

We have had some extreme infiltration with eosinophiles in cases which have been carefully worked out by cutaneous tests and found negative to the ordinary allergens, and we have found the reverse. I just wish to report that, hoping that some of the other members would be able to compare this finding with their own.

Dr. Bernhard Steinberg, Toledo, Ohio.—We were extremely fortunate not to find either clinically or pathologically any complication. The patient apparently had only the nonbacterial allergic asthma from which she died. We do not want to convey the impression that our labeling the second case that of bacterial asthma presupposes an absence of an allergic phenomenon. We are not concerned here whether there is or is not an allergic basis in those patients that begin with a bacterial infection and end with asthmatic attacks. It is, however, apparent that the pathologic changes are distinct in the bacterial type from that of the nonbacterial allergic. We are not generalizing, we cannot from two cases; we are merely presenting the pathologic changes of two asthma cases. Only the repeated reports of additional cases may justify us in establishing a pathologic entity for the conditions under discussion.

ALLERGIC BRONCHITIS*

By Geo. L. Waldbott, M.D., Detroit, Mich.

IN TICE'S *Practice of Medicine*, Cooke[1] describes a peculiar cough which he often found associated with allergic choryza. The cough is violent and paroxysmal in character and is frequently accompanied by vomiting. He states that it is difficult to differentiate this cough from pertussis and believes that it is due to hypersensitiveness that has extended to the pharynx.

In no other monograph on allergy have I found reference to this type of bronchitis with the exception of that of Duke[2] who states that many cases of allergic bronchitis are often misdiagnosed as tuberculosis, chronic bronchitis and bronchiectasis.

In a study on asthma in children A. Brown[3] asserts that a spasmodic bronchitis sometimes inaugurates asthmatic paroxysms in allergic individuals. This bronchitis is characterized by its abrupt onset as well as by its sudden subsidence. He believes that in children this bronchitis occurs more frequently than true bronchial asthma. Rowe,[4] in speaking of allergic manifestations in children, states that a dry, irritating cough is a symptom of sensitization of the trachea and the bronchi, and points out the importance of recognizing these atypical cases of asthma. Kahn[5] expresses the same opinion.

In his series of cases, Peshkin[6] found that among the factors that brought on the first attack of asthma pertussis ranked much higher than measles. Considering the fact that measles is generally much more frequent than pertussis, he remarks upon this unexpected observation. In view of the similarity of allergic bronchitis to pertussis, one is inclined to believe that some of these patients with the history of "pertussis" might in reality have had allergic bronchitis, but it was not recognized as such.

TERMINOLOGY

The lack of an uniform terminology for the various coughs observed in connection with asthma has somewhat hampered the investigation of allergic cough. The term "asthmatic bronchitis" has been employed by most writers for any cough accompanied by wheezing and dyspnea, whether allergic or not. Others (Rackemann[7]) seem to restrict this term to the emphysematous bronchitis which frequently follows asthma of long standing. One well-known author calls asthmatic bronchitis that type of asthma-like cough in which protein sensitivity is not found.

Peshkin purposely avoids using the term asthmatic bronchitis because of its inadequacy. He introduced the term "para-asthma" indicating nonhypersensitiveness in contradistinction to "asthmatic" or "hypersensitive bronchitis." However, the typical spasmodic cough described before, has not been elucidated by any of these authors.

*Read before the American Association for the Study of Allergy, Minneapolis, Minn., June 11, 1928.

CLASSIFICATION OF ASTHMATIC BRONCHITIS

The following is a classification of bronchitis occurring in asthmatics which I have found useful:

1. Para-asthmatic bronchitis.
2. Asthmatic bronchitis.

The prefix "para" indicates that this group is definitely apart from hypersensitiveness. In making the distinction between hypersensitive and nonhypersensitive bronchitis the term allergic is not used because, in my opinion, it is desirable to restrict it to the true allergic bronchitis which will be described later. Some of the factors governing the distinction between asthmatic and para-asthmatic bronchitis are allergic history, heredity, skin sensitization, eosinophilia and response to epinephrin and related drugs. Among 163 patients observed with an asthma-like cough, only 109 were thus identified as true asthmatic bronchitis. Fifty-four had para-asthmatic bronchitis on the basis of such conditions as pertussis, chronic nonspecific bronchitis, tuberculosis, bronchiectasis, cardiac asthma and foreign bodies in the lungs.

Asthmatic bronchitis itself can be subdivided into three distinct types.

A. Allergic bronchitis.
B. Intercurrent infectious bronchitis
(the common cold of the asthmatic).
C. Postasthmatic bronchitis.

ALLERGIC BRONCHITIS

Allergic bronchitis can be considered a disease entity just as any other of the allergic diseases. It is characterized by the following features: sudden onset, spasmodic, dry cough, brought on by a sensitizing substance.

If sputum is obtained, it shows many eosinophil cells and few, if any, leucocytes. The cough is relieved by epinephrin or ephedrin. The x-ray picture shows the hilum glands considerably enlarged.

In a number of cases allergic bronchitis made its appearance before the onset of asthmatic attacks. I have also observed this type of bronchitis following x-ray treatment, especially in cases which responded favorably to this measure. Moreover, it occurred following administration of other therapeutic measures such as pollen or dust extract injections. There were two cases in which allergic bronchitis preceded the onset of asthma by a period of several years.

The following are some case reports:

CASE 1.—Pla, a two and a half year-old girl, was seen at home on account of "whooping cough." This was first noticed two weeks after birth when her mother discontinued nursing her. Lately, the cough had been frequently associated with sneezing and watery discharge from the nose. The child had had eczema. The father is asthmatic. A few months ago she was troubled with violent vomiting after drinking milk. Among the noteworthy findings there was a slight dermographia, evidence of chronic tonsillitis and chronic sinusitis. The chest revealed a number of bronchitic bruits in the trachea and hilum regions, and slight hyperresonance. There was an eosinophilia of 4 per cent and a 2 plus skin reaction to cow's milk. One-half c.c. of epinephrin immediately relieved the cough

and diminished appreciably the degree of bronchitis. Upon eliminating cow's milk from her diet the child improved considerably.

CASE 2.—Way, a girl 20 years old, presented a similar condition which developed after several ragweed injections for hay fever. This cough was dry, occasionally associated with vomiting. An x-ray picture revealed marked prominence of the hilus density. Sputum could not be obtained for examination. This cough stopped suddenly with her recovery from hay fever.

CASE 3.—Ker, a ten-year-old girl, had asthma of unusual severity for seven years. Because of her failure to respond to a number of other measures, she was given x-ray treatments over the spleen. About four days after the third x-ray exposure she developed an unusually severe convulsive cough which might have been diagnosed as pertussis had it not been for the fact that the sputum contained a large number of eosinophil cells. The cough responded well to ephinephrin. After three weeks' duration the bronchitis subsided suddenly. The child has been under my observation for nearly two years. Since that time the cough has recurred twice, but she has never had another attack of asthma.

CASE 4.—Smi, a four-year-old boy, had a history of frequent severe cough which has often been associated with vomiting. The mother observed that the cough was invariably evoked by the odor of cabbage. Skin tests revealed two-plus sensitiveness to cabbage, one plus to carrots, chicken and veal. The boy's cough was temporarily relieved by avoiding these foods. However, during the following year he developed true asthmatic attacks the cause of which could not be discovered.

In addition to these, I have observed five other cases which can be classed in this group.

INTERCURRENT BRONCHITIS IN THE ALLERGIC INDIVIDUAL

Aside from the true allergic bronchitis just described, there is another type of cough which may inaugurate asthmatic paroxysms. This type may be considered as the common cold of the asthmatic and is of rather frequent occurrence. In my series of 109 patients 63 presented a definite history of having bronchitis for a short time before the occurrence of asthmatic paroxysms. It is often very difficult to draw a separating line between these infectious colds and the true allergic bronchitis because only a very few of these patients feel sick enough to present themselves for clinical studies. However, the following observations could be made on this condition. Upper respiratory tract pathology such as sinusitis, nasal septum deviation and tonsillitis was usually the source of the cough. The sputum showed a large number of bacteria of the type usually present in the upper respiratory tract. Microscopically, we found many leucocytes but rarely eosinophils. Adrenalin was of no avail, whereas the ordinary expectorant cough mixtures were useful. The patients were benefited by autogenous vaccines and by the correction of nasal pathology. Occasionally positive skin reactions for bacteria were noticed but this was not a constant occurrence. The following is the report of a typical case sensitive to food, whose attacks were always initiated by respiratory infections.

CASE 5.—Car, a twelve-year-old boy, had been afflicted with asthma since the age of three. The first attack started following pneumonia. Since the onset of the disease he had always been free from asthma during the summer months; in fall and winter the attacks occurred as often as once every two or three weeks. He had never had an asthmatic paroxysm without having previously suffered from an upper respiratory infection. The examination revealed a marked deviation of the nasal septum and chronic sinusitis, and

the lung findings typical of asthma. He was sensitive to coffee, beans and rye. The skin tests for bacteria were negative. During the winter of 1927-28 he had only one slight attack after having received a series of autogenous vaccine injections.

An account of further instances does not seem to be indicated since the occurrence of these cases is quite common.

POSTASTHMATIC BRONCHITIS

This is the type that is often falsely referred to as asthmatic bronchitis. During the chronic asthmatic state we encounter a more or less continuous cough which finally produces permanent changes in the thorax and in the lungs such as bronchiectasis and emphysema. Being invariably the result of asthma the term postasthmatic bronchitis appears to be significant. Examples of this group were seen in 15 per cent of our series. The sputum contains thick pus, sometimes Charcot-Leyden crystals and also eosinophil cells. This condition is very refractory to treatment. Epinephrin is of no value. Frequently the chronic myocardial changes are the main indication for treatment. Bronchoscopic treatment accomplishing the dilatation of strictures of the bronchial tree and the elimination of large masses of sputum may be of value.

DISCUSSION

The main purpose of this paper is to draw attention to the relatively frequent occurrence of the true allergic type of bronchitis. It is of paramount importance to recognize it as such among similar conditions, because one might thus be enabled to detect bronchial asthma in its earliest manifestations. Moreover, by being aware of the similarity of allergic bronchitis to hilum tuberculosis and pertussis one might guard against the serious consequences arising from misdiagnosing these conditions.

The classification of asthmatic bronchitis into the three types is recommended mainly for therapeutic reasons. We have seen that removal of sensitizing substances, epinephrin and all the other measures which are applied for asthma are of great benefit in treating the first type, the true allergic bronchitis. For the second type, the intercurrent bronchitis of the asthmatic individual, vaccine treatment is indicated because these "colds" are of infectious character. Hygienic measures as usually advocated for the common cold and removal of chronic upper respiratory pathology might aid materially in the treatment. The type most refractory to treatment is the postasthmatic bronchitis in which permanent pathology of the lungs and heart is present.

SUMMARY

1. A certain type of bronchitis is described occurring in hypersensitive individuals which differs from the common infectious bronchitis. It is characterized by its sudden onset, by dry unproductive cough and by response to epinephrin and ephedrin. It is elicited by substances which are known to cause asthmatic attacks. This cough sometimes inaugurates asthmatic attacks and occasionally occurs before the subsidence of asthma and hay fever. In several individuals with inherited hypersensitiveness it was found as the only sign of their allergic constitution.

2. Aside from the occurrence of allergic bronchitis a great many asthmatics suffer from a bronchitis which clinically is distinct from true allergic bronchitis. This condition presents the features of the common cold and is termed "intercurrent bronchitis of the asthmatic."

3. A third type of bronchitis, the postasthmatic bronchitis, is described. It follows asthma of long duration and is often associated with permanent changes in the lungs due to allergic asthma.

4. In order to avoid ambiguity, to further better knowledge concerning etiology and for the sake of a rational therapeusis, the term asthmatic bronchitis should be restricted to the hypersensitive individual. Para-asthmatic bronchitis is suggested for the nonsensitive asthma-like cough.

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DISCUSSION

Dr. Albert H. Rowe, Oakland, Calif.—I have been interested in this group of patients with allergic bronchitis for some time. I am very sure that the speaker is correct in stating that there is a definite type of bronchitis due to allergy. These patients may not show any asthmatic symptoms at all. I have in mind one little girl who came to me some three years ago. She was about nine years old at that time, having had a cough all her life since birth. The parents had moved over various parts of the country to give relief to the child, but without success. I did skin tests on the child and they were all negative. The child had a definite history of dislikes for certain foods. The mother had forced her to eat foods she disliked, which was very unwise.

By the use of "elimination diets," I found the child was sensitive to both wheat and milk. The child's cough stopped within four or five days after she was taken off wheat and milk. She got along very well for about six or seven months and at that time, the mother thought she was so well she could return to the use of wheat and milk, and when she did, the attack returned, and again was promptly stopped by the elimination of the foods. During that month's interval the child had been under the care of another physician, who treated her from the point of view of bronchitis, with steadily increasing trouble instead of improvement.

That is just one of the many experiences I have had in regard to this so-called allergic bronchitis. I think it is a term which is quite important to put into the literature and for us as allergists to recognize, a type of cough, bronchitis which is due to definite allergy, without asthmatic symptoms.

Dr. Alexander Sterling, Philadelphia, Pa.—May I ask how many of these series were tested and how many were sensitive or gave allergic skin reaction?

Dr. M. Murray Peshkin, New York City.—I am very sorry to have heard Dr. Waldbott employ the term "para-asthma" in his classification of asthma in a different sense than the original definition that I introduced in 1926. I plainly indicated then that the term

"para-asthma" was introduced as a substitute for the more objectionable term "obstructive asthma." It covers the type of asthma in which there exists a definite pathologic condition within the chest inducing tracheal or bronchial stenosis.

Before the subject of allergic bronchitis can be intelligently discussed, one must satisfy himself just what definition is to be applied to "asthma." Asthma is a clinical syndrome, quite readily diagnosed on physical examination of the patient. The diagnosis once made, all investigators of this disease proceed to search for the etiologic or exciting factors responsible for the presenting symptoms. Some authors would restrict the term asthma only to those patients exhibiting protein hypersensitiveness. Such a point of view is erroneous, since asthma, as far as children are concerned, is nothing more than a recurring dyspnea, more marked in expiration associated with wheezing, and the exciting cause may or may not be protein sensitization. Thus in the light of the present knowledge of allergy, the old definition of asthma is untenable since it only considers the attack as all-important. Physicians are learning more and more how to recognize diseases in their incipiency. The early manifestations of asthma especially in children are definitely recognized as consisting only of recurrent spells of wheezing. To this incipient stage of asthma the diagnosis of acute bronchitis or asthmatic bronchitis is too frequently and erroneously applied. The attack itself is merely the final stage of the asthmatic state. A positive diagnosis of pure allergic bronchitis in children therefore can only be applied in those patients presenting symptoms of bronchitis in the absence of wheezing and in whom protein hypersensitiveness has been demonstrated.

Several years ago Dr. George G. Ornstein of New York called attention to a seasonal type of allergic bronchitis of pollen etiology. Dr. Waldbott's report is of interest because he has presented facts which are of extreme clinical importance. Allergic bronchitis may occur independently of the asthmatic state or it may occur during the intervals of freedom from symptoms of asthma. This condition is more readily demonstrated in children than it is in adults.

Dr. I. S. Kahn, San Antonio, Texas.—I don't think we shall have to. I have on several occasions desensitized perennial hay fever in children with pollen. By unintentional overdoses of pollen extracts, I have produced this intense, annoying cough which is almost identical to pertussis, which dragged on ten days or two weeks unless adrenalin was used to check it up. In a community such as mine, where we have a good deal of pollen work particularly, with pollen hay fever and asthma, take a family of four children, and if you inquire into the family, you will find one child who is bothered with nasal trouble and a cough. I get a chance every now and then to prophesy such and such a child will develop into asthma and they usually do. I have seen this condition in adults, not by overdoses but actually in nature.

I had a case last year, a business man from New Orleans who came to San Antonio because of a chronic cough. The x-ray did not show anything. He had had hay fever which had stopped some ten or twelve years previously, and there had been no hay fever during that time. His skin tests were positive for pollens. I put that man in a pollen-free room and in about five or six days that terrific annoying cough that had gone on for about ten years, was about gone. So we will, once in a while, run into these cases in adults as well as in children.

There seems to be an intermediate stage between hay fever and the actual bronchial asthma type, whether it is tracheitis or bronchitis.

Dr. George L. Waldbott, Detroit, Mich.—I am sorry that Dr. Peshkin seems to have discarded his term para-asthma. Since there is such a widespread confusion on the subject of allergy due to inadequate terminology, I feel that this term is indicated. The prefix "para" means something aside from true allergic asthma. I thought it logical that any wheezing and dyspnea that is not allergic asthma should be termed para-asthma. I should have been interested in hearing this question discussed by some of the other men.

In regard to Dr. Sterling's question, I wish to say that I have had ten cases, among which three gave positive skin tests. However, in others the history definitely revealed

sensitiveness although the skin tests were negative. For instance, one patient (J. K.) had severe allergic bronchitis whenever she ate cantaloupe.

One point which I should like to stress, is the fact that I found marked enlargement of the hilum glands in most of the cases. Cooke, in his monograph in Tice's Practice of Medicine, states that he observed enlargement of the tonsils in a patient showing the dry cough which I have termed allergic in my discussion. Since the tonsils are composed of the same tissue as the hilum glands, one is inclined to think that enlargement of the lymphoid tissue may have some bearing on the causation of the cough.

INCIDENCE AND SIGNIFICANCE OF NEGATIVE SKIN TESTS IN POLLEN ASTHMA IN INFANTS AND YOUNG CHILDREN*

By I. S. Kahn, M.D., and Emma M. Grothaus, San Antonio, Texas

EVERY possible effort was made in this series of cases to eliminate all cases of nonpollen etiology. Cases giving positive skin tests to our other known specific etiologic antigens or clinically responding to nonspecific factors, as many of them did, were considered to be of additional pollen etiology only after the following conditions had been observed:

1. A definite history of seasonal and locational variations in the attacks.

2. Failure to secure results by the elimination of nonspecific and specific positive skin test factors other than pollen.

3. Relief of the asthma during a possible causal pollination season without the use of other measures than the pollen precautions we have described elsewhere.[1]

4. Recurrence of the symptoms following the experimental relaxation of these precautions.

5. Induction of the usual cutaneous response and some nasal or bronchial allergic symptom indication by the subcutaneous pollen tests,[2] or by direct ocular or nasal application of pollen extracts or pollen, corresponding to the history, with negative controls to other pollens.

The pollens employed were the usual of the eastern half of Texas, ragweeds, grasses, carelessweed, and mountain cedar. Testing was intradermally done with 1:50 extracts in Coca's[3] or Stier's solutions,[4] after preliminary testing with weaker dilutions. We have not had enough experience to state whether stronger extracts would reveal any differences in the figures to be quoted.

A wheal accompanied by pseudopodia, however small, was considered a definite positive skin test. Wheal and erythema formation, without pseudopodia, were considered questionable reactions.

In studying the tables to be presented, due consideration must be given to the fact that my community is one of almost constant high atmospheric pollen concentration, where, as revealed by almost daily examination of pollen plates over a number of years, there exists never over a week in the entire year with-

*Read before the American Association for the Study of Allergy, Minneapolis, Minn., June 11, 1928.

out the presence in the air in considerable abundance of some highly antigenic pollen. With our mild climate, and resultant constant outdoor, open window existence, with our low annual rainfall and frequent high winds, naturally pollen, as the sole or as a complicating factor in bronchial asthma, would be plausibly of high percentage frequency, and as a matter of fact does enter into the etiology of at least 90 per cent of the cases we see.

Pollen ceases to be a factor clinically, either temporarily or permanently as the case may be, in many of my cases who return to or visit more northerly communities of lessened pollen concentration and shorter seasonal duration. Whether any such percentage figure of negative skin tests as are here presented exists elsewhere, we are not prepared to say.

As seen from Table I,[5] pollen asthma may start very early in life.

TABLE I

AGE OF SYMPTOM INCIDENCE IN 100 POLLEN ASTHMA CHILDREN

1 mo. or under	1	
1 to 6 mo.	2	
6 to 12 mo.	7	
1 to 2 yr.	22	
2 to 3 yr.	17	In 5 of these cases hay fever
3 to 4 yr.	17	symptoms existed from birth.
4 to 6 yr.	15	
6 to 8 yr.	8	
8 to 10 yr.	7	
10 to 12 yr.	4	

A definite history of heredity was secured in 80 per cent of these cases. If we take into consideration the fact that pollen asthma in children is usually preceded by months or years of vasomotor rhinitis and recurrent bronchitis, febrile or otherwise, and that in 48 per cent of this series of cases, asthma started before the end of the third year, then our only possible conclusion is that pollen hypersensitiveness in many instances approaches the point of being natal or even suspiciously prenatal.

The percentage of positive skin tests according to the age of the child when first seen is of no value as such testing might have been performed after a history of asthma varying from a few days to the age of the child. However, in studying this relationship to the duration of the asthma, as shown by Tables II and III, a very interesting state of affairs is revealed.

It will be noticed at once that there is a sharp difference in the percentage of positive and negative skin tests in Tables II and III. In the children in whom asthma had recurred for a period of seven years or more, the percentage of questionable or negative skin tests was negligible, while in children whose asthma had lasted six years or less, the percentage reached the respectable figure of 40 per cent, and in infants and children up to two years of age equalled the number of positive tests secured.

The idea that the intracutaneous test with serial extract dilutions is a reasonably satisfactory measure for determining the degree of pollen hypersensitiveness existing in a given individual has been rather generally adopted by allergy workers. Accepting this idea, which on the whole and with rare exceptions that need not be referred to in this connection, as correct, it will

TABLE II

RELATION OF POSITIVE CAUSAL POLLEN SKIN TESTS TO DURATION OF ASTHMA IN 88 CASES

	POSITIVE	QUESTIONABLE	NEGATIVE
1 mo. or less	1	1	0
3 mo. or less	1	0	0
4 mo.	1	1	0
6 mo.	1	1	1
9 mo.	2	0	2
1 yr.	5	4	2
2 yr.	2	2	2
3 yr.	7	3	3
4 yr.	7	0	1
5 yr.	5	2	1
6 yr.	7	0	4
Total 6 years or less	39	14	16

TABLE III

RELATION OF POSITIVE CAUSAL POLLEN SKIN TESTS TO DURATION OF ASTHMA IN 88 CASES

	POSITIVE	QUESTIONABLE	NEGATIVE
7 yr.	10	1	0
8 yr.	3	0	0
9 yr.	1	0	0
10 yr.	1	0	0
11 yr.	1	1	0
12 yr.	1	0	0
Total 7 yr. or more	17	2	0

be noticed that, barring individual variations which must always occur in a statistical study of this kind, the degree of sensitiveness increases in a heavy pollen environment directly in proportion to the duration of the disease. If this be true, then the negative skin tests secured in pollen asthma in infants and young children must be due, not to any technical difficulties in testing or any differences in the reactive response between the skin of the young child and the adult, but to a degree of sensitiveness less than that possible for the skin to detect with our present methods. Such cases in the South in adults are not particularly uncommon.

If negative skin tests to 1:50 extracts in infants and young children are due in many instances to a low degree of hypersensitiveness as suggested, with symptoms due to high pollen dosage, then by proper precautions against pollen overdosage alone, without the institution of other measures, the reception of atmospheric pollen might be held down to a point well inside this high tolerance limit, with either complete freedom from respiratory allergic symptoms or holding such symptoms correspondingly down to one or two light annual attacks following exposure to extremely heavy atmospheric pollen concentrations, yielding at once to ephedrin, and not worth the efforts or expense of specific desensitization. The practical methods of accomplishing this end have been described elsewhere.[1]

We have at the present time 40 cases of early pollen asthma in children who have been handled with these pollen precautions alone without other measures for periods of from six months to two years. All have shown improvement, and in 75 per cent the results have been all or even exceeded what was aimed at. Several cases with typical positive skin tests to 1:50 extracts

are included in this series. In cases reacti ngpositively to 1:500 extracts, we have feared to try this line of treatment, and proceed at once to usual desensitization methods. Fortunately infants and young children with early asthma, as has been seen, seldom fall in this latter class. One case with insufficient improvement was found much more sensitive by subcutaneous tests than what the intradermal results would have indicated, showing that this method of hypersensitivity determination by intradermal testing is not absolutely infallible.

In addition to the above, six children seen with symptoms for the first time during the 1927 ragweed pollination season, cleared at once and were kept perfectly clear throughout the entire season by this method of handling without medication of any kind.

For the last two years we have made it our business to ask of every adult patient under treatment for pollen hay fever or asthma, the number of children in the family and whether any showed symptoms possible of being construed as preasthmatic vasomotor rhinitis or bronchitis. A number of young children were thus found and the diagnosis of such preasthmatic state easily confirmed by the prompt and continued response to these antipollen precautions with complete immediate clearing of preexisting symptoms.

CONCLUSIONS

1. Negative skin tests are comparatively frequent in infants and young children suffering with bronchial asthma of pollen etiology.

2. These negative skin tests apparently indicate a low degree of hypersensitiveness.

3. Advantage can be taken of this low degree of sensitivity to secure successful clinical results by proper prophylactic measures without the institution of specific desensitization.

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DISCUSSION

Dr. Milton B. Cohen, Cleveland, Ohio.—I am very much interested in this question of classification of hay fever by means of the strength of solution producing reaction, and I agree with Dr. Kahn that it cannot be done practically. I cannot classify cases as a, b, c, and d. Cases who give a definite reaction to pollen today may have a negative reaction on their skin tomorrow.

I have a case in point that I studied just two weeks ago. We do not see very many cases of pollen hay fever and asthma in our hospital as these are ambulatory cases. We were fortunate enough to have one admitted that I had studied some two or three years previously and knew to be sensitive to grass and ragweed pollen, and also to orris root. I had tested this patient one week previously to all three of these substances. I wished to demonstrate for the benefit of the interns who had not seen the reactions, so I made three scratches on the arm. To my chagrin, all of the skin tests were completely negative. We repeated the tests again on the next day and they were still negative.

We bled this patient on the day the skin tests were negative and passively transferred, to a patient who was normal. In the passively sensitized areas we demonstrated reaction to Timothy, Ragweed and Orris root. Thus the blood from a skin test negative patient proved to contain allergic antibodies. If such things occur, how can we classify the severity of hay fever by the amount of pollen producing reaction.

I think very often we are inclined to be led astray by the fact that we feel that a positive skin test has definite clinical importance, and we are led astray also when we feel that a negative skin test means that the individual is not sensitive to some particular substance. We must remember always, we all make this same mistake, and have to be constantly on guard against it; that every skin test is only a clue and it must be checked by clinical experimentation before we know what it means in any patient.

I think the method Dr. Kahn talks of, pollen precautions, is a method of extreme importance, but I shall not discuss that in detail now because I shall talk about it tomorrow, but a great many of the patients with hay fever who have mild hay fever can be relieved merely by proper pollen precautions without any need of preseasonal injections.

Dr. Warren T. Vaughan, Richmond, Va.—Possibly similar types of cases exist in Virginia, but if they do I have not found them. I have, of course, seen negative food reactions.

The difference, presumably, is in the difference in pollen prevalence. We have a low pollen prevalence and we are more likely to get hay fever only in those who give good skin test reactions.

I feel that this paper emphasizes beautifully the value of these annual round table discussions in showing the great geographic difference in the etiology and the manner of treatment necessary in the allergic diseases.

Dr. M. Murray Peshkin, New York City.—Dr. Kahn's work has been of special interest to me because independently of each other we have been studying refractory sensitizations in children. In New York City the pollen concentration is considerably lower than that in San Antonio or Oklahoma City. Yet each year about 8 per cent of the children with asthma show negative pollen skin tests with positive histories of pollen sensitiveness. A child is considered skin refractory to pollen when both the scratch and intradermal tests are negative. For the scratch tests pure pollen is employed and for the intradermal tests fluid extracts in concentrations of 1-50 and 1-20. A positive diagnosis is readily made by the ophthalmic tests which consists of placing pure pollen on the conjunctiva of the lower lid. In the residential sections of midtown New York the houses are tall and built closely together so that the avenues appear not unlike small canyons. Yet in spite of the low pollen count the patients who are skin refractory residing in such environment have at times severe pollen asthma. It is also of interest to note that in order to confer immunity on this type of patient a maximum dose of 1 c.c. of a 1-50 extract of pollen must be administered.

Dr Kahn is to be congratulated for his intense and continued interest in this special phase of allergy because it forces to the realization that a test must also be developed that will aid in definitely diagnosing those cases whom are refractory to food and inhalant substances. At present such cases are labelled nonprotein sensitive. Pure pollen is soft and contain no chemical irritants thus making it suitable for conjunctival testing. Besides, the pollen eye tests which react negatively serve most admirably as controls. Because of the nonspecific irritation induced by most of the food and inhalant powdered proteins these substances cannot be employed for eye tests.

Dr. I. S. Kahn, San Antonio, Tex.—This paper was a sort of an entering wedge to try to find out why negative skin tests occur. I have done most of my work with pollen because so many of my cases are pollen cases. A question comes up as Dr. Peshkin says, if we can have pollen cases with negative skin tests, why cannot we have animal hair, feather and food cases with negative skin tests? Probably we do. Certainly I have seen a number of food cases, definitely clinically worked out as food cases with absolutely negative skin tests.

If we go on the bases in this asthma work that we are going to depend on skin tests alone to guide us for diagnosis, we are going to make mistake after mistake. For instance, that child which I showed on the record with positive skin tests to food, animal hair, and negative pollen tests, was a definite pollen case clinically. One of the reasons we make mistakes on our asthma cases today is the fact that we pay strict attention to our skin tests and nothing further. We go to work and say because a case is positive to feathers and negative to pollen, it must be a feather case. I did that too until I had some disasters and failures.

I do not know so much about northern cases as I do about those in the South, but I live in a health resort and cases float into San Antonio from all through the north, and you would be surprised at the number of negative pollen skin tests in chronic asthma cases that I see in San Antonio that originate in Chicago or any of the northern cities. The eye test of Dr. Peshkin with crude pollen has proven extremely valuable in my work, and it seems specific. However, it is not an infallible test. In Texas, with the cases I see, it will clear up fifty per cent, that I have to find out by the subcutaneous or some other method of testing.

SOME CAUSES FOR FAILURE IN THE SPECIFIC TREATMENT OF ALLERGY*

By Warren T. Vaughan, M.D., Richmond, Va.

A GUNN AULD[1] in the *British Medical Journal* for February 4, 1928, speaks of the so-called specific treatment of asthma as follows: "It may be said that the method has largely broken down. Nevertheless a clear light has been thrown on the *modus operandi* of many of these substances and some excellent results have been obtained so that it is unjust to depreciate it. It is a distinct advance in our knowledge and the time may come when definitely specific cases can be made to respond more to specific therapy though at present a considerable number do not do so." Auld refers I take it not only to desensitizing injections but also to protein avoidance and to the value of skin tests in general. Men like Coke in England, and others on the Continent, such as VanLeeuven, in Holland, and Giani, in Italy, have become convinced of the value of specific methods of examination and therapy. But on the whole the continental attitude has been one of some indifference.

In this country on the contrary there are many of us who firmly believe that with this method of approach we have already passed the stage where we wonder whether the method will work in the individual case, and have reached a point where we are vexed and perplexed when it does not work and proceed at once to find the reason for its failure.

In this paper I offer a brief discussion and classification of some of the causes for therapeutic failure which I have encountered. At the same time I have not hesitated to draw freely on the experiences of others so that the discussion might be made more complete.

Robert Hutchinson,[2] in his recent masterly discussion of the principles of general diagnosis, attributes poor results to (a) defective observation, (b) defective knowledge or (c) defective judgment. He says, "It is commonly said that more mistakes are made from not looking (defective observation) than from not knowing (ignorance). However this may be I believe that still more mistakes arise from bad weighing of evidence (lack of judgment)." These remarks may well be applied to the study of allergy. Following the same line of thought, I would offer four general reasons for therapeutic failure, namely, superficiality, ignorance, poor judgment, and insurmountable obstacles.

SUPERFICIALITY

The superficial thinker and investigator will meet with little success in the specific study of the allergic diseases. The successful allergist or immunologist or whatever you choose to call him must be the very impersonation of the question mark and in his travel with his patients along the road to

*Read before the American Association for the Study of Allergy, Minneapolis, Minn., June 11, 1928.

understanding must be willing to journey down many a seductive appearing by-path, chasing many a will-o'-the-wisp in order to be certain that no discovery of real significance will be overlooked. Fortunately there is usually no great hurry. The patient has had his disease for many years and is well content to allow ample time for thoroughness provided he has reasonable assurance of ultimate relief. Not only must the allergist be diligent, he must also possess a ready imagination. He must look upon all things in the immediate and remote environment of the patient as potential allergens even though they be so minute as to be invisible under the microscope or so apparently innocuous as mounted moose heads or chocolate coated pills.

The rôle of the allergist is that of a detective. His client has lost something, his health and sense of well-being. He is able to give some clues but it is up to the examiner to ransack the history of the past, even including the experiences of remote ancestors, and to make a most painstaking examination at the site of the loss and throughout the surrounding territory so that he may leave no clue untouched in his effort to return good health to his client. No clue is too insignificant to be carefully studied in orderly arrangement with the other clues.

IGNORANCE

Ignorance is quite a different attribute from superficiality. Neither is an insurmountable obstacle. I refer here not to the ignorance which accompanies lack of interest but to the ignorance caused by our lack of understanding of the fundamental processes of allergy. Twenty years ago our ignorance of the allergic aspects of asthma, hay fever, eczema and the other diseases may be said to have been complete and it is reasonable to assume that as time goes on our knowledge and understanding will be steadily enhanced. Ignorance may be properly subdivided into ignorance of allergy, that is, ignorance as to the basic processes involved; ignorance of allergens, that is, failure to recognize certain substances as potentially allergenic and failure to understand the exact nature of allergens; ignorance of technic which in the hands of the best is undoubtedly responsible for a percentage of failures; and ignorance of the patient, failure to realize that we must deal not only with the seed of the disease but also with the soil in which it falls and that each patient is constituted differently.

IGNORANCE OF ALLERGENS

Our ignorance of allergens is due in part to feeble curiosity and poor imagination and in part to our uncertainty as to the exact nature of allergens and what varieties of reagents this class may include. It requires a nimble thinker to demonstrate the allergenic rôle of such substances as grain dust, moulds, intestinal parasites, moths in feather pillows, sparrows nesting outside the bedroom window, hog bristles, and urease. Even with such rare causes the intelligent patient will often himself give the clue but frequently we are not alert enough as to the possibilities to follow it up.

Let me propose a tenet and be bold enough to call it an axiom. There is a specific allergenic cause for nearly every case of true allergy. Failure to

find the allergen does not demonstrate its absence. If we will doggedly persevere in our search for the specific cause after the usual possible causes have been ruled out, we will materially reduce the proportion of our failures.

A most stimulating experience along this line has been related to me by Dr. Earl D. Figley, of Toledo, Ohio. He tells of an asthmatic in whom he made a most exhaustive search for the etiologic factor even to the point of visiting the home and making extracts of a long list of substances in the house but without avail. Many months later Dr. Figley[3] was investigating the possible cause for attacks of asthma in a group of individuals living in the neighborhood of a castor oil factory. He obtained some of the dust from the castor bean and most of the asthmatics in the neighborhood were found strongly sensitive thereto. Many other asthmatics living within a radius of one or two miles of the plant then came in for testing and among them Dr. Figley found his old friend. He was sensitive to the dust of the castor bean.

I have a horse asthmatic who is never near horses but who will develop an attack when her brother sits beside her at the dinner table, after a horse back ride. This is avoided when he changes his clothes prior to dining. Here we might borrow from the bacteriologist and speak of a carrier state. A third individual is responsible but the contact with horse epidermal protein is just as actual although more difficult to trace than it would be did the asthmatic work in a stable.

Balyeat[6] whose botanic survey of Oklahoma has been most comprehensive has convincingly demonstrated the need of accurate knowledge of the local botanic flora in the patient's immediate environment. Even in the single state of Oklahoma the predominating etiologic pollen may be quite different in different counties. But before this could be known and applied laborious weeks were devoted to the study. Prior to his classification I dare say that some cases were considered unsuccessful because the right pollen was not available for testing.

The first battle cry of the allergist should be, "The specific allergen is there, somewhere—find it! Where there are several find the right one."

I have found the accompanying questionnaire of some help in finding the cause in the occasional obscure case, and in establishing the probable allergic nature of the disease. The discussion of each question with the patient occasionally brings to the surface a suggestion of real value in our search for the cause. It is what we all do in a more or less routine manner but possesses the advantage of a somewhat orderly and quite inclusive classification.

IGNORANCE OF ALLERGY

Just when we have about concluded that we understand the nature of allergens some new evidence is put forward to again effectively spread the shadow of doubt. There is so much evidence that allergens are protein in nature that we become rather disconcerted when Grove and Coca[4] suggest and are supported in their suggestion by Black[5] that pollen and dust allergens are probably not nitrogenous. We have tried to explain drug idiosyncrasies in terms of the usual concept of protein allergy but the fact remains that these

nonprotein substances may produce the symptoms of allergy. A physician in my experience, in his thirties, began having attacks of asthma whenever he would open an ampule of neoarsphenamine. He had never had asthma before and no other substance appeared to precipitate attacks.

As time goes on new observations will require new explanatory hypotheses. Therapeutic efficiency depends in great part on the correctness of our understanding of the malady.

IGNORANCE OF TECHNIC

Inefficient testing and with defective material is responsible for a proportion of false negative results. The potency and durability of test materials are gradually being enhanced. New methods of preparation, such as that described by Peshkin[7] for dust extract or that by Stier[8] for glycerine extracts, will enhance our diagnostic efficiency. Even in the matter of reading the reactions there is still some room for discussion. Kahn[9] has emphasized the importance of testing with highly concentrated pollen extracts even using the ophthalmic and the subcutaneous method, as a requisite for best results in the very mildly sensitive pollen case in territories where pollen abundance is unusually great.

In my own work I have stressed the value of delayed reactions after four to six hours and after twenty-four hours. These have not the same value as the immediate reaction but the delayed reactions have not infrequently given me the clue as to the allergenic factor when the immediate reaction alone would have failed me. In one series[10] of benefited cases my diagnosis was made on the delayed reaction alone, in 17.9 per cent. But many do not apply the test in a way to best bring out the delayed reaction. Thomas[11] speaks of making scratches one-sixteenth inch long. This may be enough to elicit the immediate reactions in favorable cases but if the delayed reaction to foods and epidermals is to be easily identified the scratch should be longer. My scratch is usually about three-eighths of an inch long. It is made almost invariably on the back where it will not show. Even with the immediate reaction the probability of getting sufficient protein in contact with the tissue cells is greater with a longer scratch.

The reaction which is no better than borderline, but which shows up as borderline on two or more of the three readings is worthy of consideration. Thirty-four per cent of my cases showing only borderline reactions obtained satisfactory relief from[12] protein avoidance.

And there are still some who in the face of a negative cutaneous reaction and in the face of a most suggestive history are yet content to consider this negative information conclusive and fail to follow it up with intradermal tests in increasing concentration.

Probably many of the proteins with which we now get negative reactions will be fractionated as has been done in the case of the wheat protein, and we will find positive fractions of negative wholes. Bernton[13] has described such an experience in the case of bean.

One important potential source of technical error has recently been emphasized by Thomas. Adrenalin or ephedrin administration shortly before the performance of the sensitization tests will give false negative skin reactions. In those cases in which it is necessary to perform the test while the patient is still suffering from an acute attack it is better to use a temporary palliative, such as codeine or morphine, for relief during the test.

The technic of specific desensitization is now quite different from what it was even five years ago. Further technical improvements will improve our results.

IGNORANCE OF THE PATIENT

We now come to a most important potential cause for therapeutic failure, namely, ignorance of the patient. The allergist like all other students in limited lines of medicine and surgery is prone to develop a one-sided outlook. It is quite legitimate to start the patient out on protein avoidance or protein desensitization alone. Indeed, this is the ideal procedure for if this is accompanied by a lot of other nonspecific treatment the uncertainty will remain as to whether the specific treatment was successful and should be persisted in. It is likewise desirable, in the event of failure, to carry the search for specific allergens as far as possible before resorting to nonspecific therapeutic methods. But in the event of failure one must not lose sight of the fact that we are dealing as we might say with a chemical reaction in which there are two reacting substances, the allergen and the patient and that the latter is as worthy of study as the former.

Does the child run a fever with its asthmatic attacks? Look for a mediastinal tuberculous adenitis or even for parenchymatous tuberculosis. Are the attacks apt to come on in the evening or shortly after retiring? Remember that they are more severe when the stomach is full, as after the evening meal. By the same token, recall that the old country doctor often achieved quite a measure of relief by giving enemas. From what other pathologic conditions is the patient suffering? Bear in mind that the patient may be in allergic equilibrium or balance even while he is in contact with small amounts of specific allergen and that the evidence would indicate that this equilibrium may be overthrown not only by increasing the allergenic contact but also by the action of any of a wide variety of nonspecific factors. Is he constipated? Forty-three per cent of my allergics who were not benefited were chronically constipated. Only 37 per cent of those who were benefited were constipated. What about focal infection? Of those benefited 70 per cent showed one or more foci of infection while of those not benefited 82 per cent had focal infection.[12] These figures are to be compared with the conclusions of the Life Extension Institute that 85 per cent of adults examined showed some focal infection. Theirs was not an allergic series. Is there a thyroid deficiency? Is the baby teething? Recall Walker's case[14] of a man who was relieved of his asthma by herniotomy, with return upon return of the hernia and relief again after a second operation.

What is the condition of the patient's nervous system? Duke[15] has emphasized the importance of the nervous and mental factors. Relief obtained from

cocaine application in the nose is quite real when it does occur and its action is probably upon the nerve endings. Does vagotonia or sympatheticotonia or better dystonia or imbalance between the two systems play a rôle irrespective of allergenic contact? There is much evidence that it does. Simple fright in an allergic individual may bring on an attack. Often we do not give enough attention to the so-called asthmatic habit. The occasional morphine addict, made so in his search for relief from asthma can stir up a real good attack with wheezing râles through the chest when he enters a new doctor's office to beg anew for the soothing poppy. One of my most resistant asthmatics tells me that after she has been able to do without adrenalin for three or four days, she tries to fight the next bad attack rather than use adrenalin, for she has discovered that if she can stick it out through the night the following night is likely to be better. If she does not, she usually requires adrenalin on the second night also.

Is mechanical irritation interfering with the results in a case of eczema? A woman with seborrhoic eczema of the forehead, two plus sensitive to lobster, pyrethrum, pepper and one plus to lactalbumin, cocoa, rice, celery and strawberry and with a clearcut allergic history in that tomatoes cause urticaria, strawberries produce "ptomaine poisoning" and she has frequent attacks of vasomotor rhinitis, was placed on specific food avoidance without recognizable benefit to her eczema. The next question was is this a true eczema or is it a seborrhoic dermatitis possibly dependent upon trichophyton infection. A soothing parasiticide ointment containing sulphur was prescribed. The eruption on the forehead cleared up promptly. Conclusion—diagnostic error! But no, as soon as she started in again with the ingestion of milk the rash returned as bad as ever. This disappeared again on milk avoidance but the ointment was continued.

A local physician tells me of a family with several asthmatic children the father of whom many years ago had had syphilitic infection. He assures me that he is able to keep them all asthma free by employing periodic mercury inunctions.

What of the infection factor? Whether or not we side with those who insist that one may be specifically sensitive to the protein of specific bacteria, it is a fact that one way or the other infection plays a part in upwards of 40 per cent of asthmatics. If we deny that infection plays a part we are left helpless in the treatment of too large a percentage of asthmatics. We need not take sides in the issue over specific bacterial sensitization unless we care to but the occasional spectacular relief after autogenous vaccine therapy compels us to consider infection while considering the patient as a whole.

POOR JUDGMENT

Fortunately experience will ripen judgment. One who has had any wide experience with hay fever is not likely to emulate the tyro who because a person is suffering from late summer and autumn hay fever tries ragweed desensitization in spite of the fact that the symptoms begin around August first. But allergy is a great field for speculation and most of us have our

The Vaughan-Graham Clinic, Richmond, Va. *Asthma and Hay Fever Detail*

Name _____ Date _____

Identification
- Asthma
- Bronchitis
- Croup
- Pneumonia
- Hay Fever
- Sneezing
- Colds
- Coughs
- Wheezing
- Nasal obstruction
- Stuffiness
- Sinus trouble
- Itching palate
- Itching eyes
- Itching nose
- Itching throat
- Itching ears
- Itching larnyx
- Lacrimation
- Olfactory impairment
- Taste impairment
- Diurnal variations

Associated conditions
- Eczema
- Urticaria
- Pruritus
- Other eruptions
- Headaches
- Migraine
- Food upsets
- Ivy poisoning
- Urinary frequency
- Asthenia
- Hypotension
- Colitis
- Epilepsy

Family History
- Asthma
- Hay Fever
- Rhinitis
- Urticaria
- Eczema
- Skin disease
- Headaches
- Migraine
- Food upsets
- Colitis
- Ivy poisoning
- Hypotension
- Epilepsy

Contributing factors *Sneezing* *Asthma*
- Chilling
- Electric fan
- Draughts
- Dust
- Smoke
- Tobacco
- Flowers
- Face powder
- Odors
- Perfumes
- Soap
- Crowds
- Theatres
- Coryza
- Drugs
- Animals
- Pets
- Furs
- Bedding
- Catamenia
- Exhaustion
- Shock
- Specific localities
- Change of locality
- Constipation

Foods
- Suspects
- Symptoms
- Dislikes
- Symptoms
- Cravings
- Combinations
- Overeating
- Previous diets
- Results

Climatic
- Season
- Altitude
- Temperature
- Humidity
- Wind direction
- Light
- Specific localities

Bedroom
- Always same room
- Attacks elsewhere
- Sleep alone
- Room alone
- Pillow
- Mattress
- Covers
- Wall coverings
- Rugs
- Pets
- Ventilation
- Plants

Home
- Describe house
- Time living there
- Heating plant
- Dust
- Cleaning methods
- Suspect rooms
- Pets
- Mice
- Flowers, etc.

Grounds
- Flowers
- Weeds
- Pets
- Live stock
- Contents of barn

Neighborhood
- Time living there
- Other cases
- Their causes
- Trees
- Plants
- Fields
- Weeds
- Insects, etc.
- Factories
- Smoke
- Odors

Occupation
- Detail
- Contacts
- Ventilation
- Dusts
- Flowers

Miscellaneous
- X-ray chest
- X-ray sinuses
- Other X-rays
- Gastric Analysis
- Remedies tried and Results

Nose and Throat Operations

OPERATION	DATE	REASON	RESULT
1.			1.
2.			2.
3.			3.
4.			4.

Remarks:

pet theories. Occasionally in our enthusiastic support of an as yet unproved theory we fall into the rut of following some special line of therapy in the hope of proving our point, and fail to observe that too large a proportion are not obtaining the relief which reason and experience have shown may be obtained by the more usual methods. No use to try to treat all asthmatics with tamponage of the ethmoids when your better judgment will tell you that not all are infectious in origin and that an edematous nasal mucosa does not necessarily indicate local bacterial invasion. Why treat an asthmatic with extensive bronchitis and bronchiectasis only by specific protein avoidance or desensitization and hope for best results when you must know that appropriate nonspecific methods must be applied to the other local pathology for greatest relief?

INSURMOUNTABLE OBSTACLES

Insurmountable obstacles beyond any that might fall in the preceeding categories will prevent best results in some cases. Pronounced pulmonary emphysema, advanced bronchiectasis and some cases of sinusitis will fall into this group. But good judgment and increasing knowledge will eventually reduce the total number of insurmountable obstacles.

NONCOOPERATION

Noncooperation on the part of the patient or the referring physician is sometimes a cause of failure. The better the patient understands the rationale of treatment the more willing he usually is to cooperate. Physicians who have not made a special study of asthma sometimes do not seem to understand complete avoidance or to appreciate its importance. All of us I am sure have had new patients assure us that they had completely avoided wheat or orris root or feather dust, only to discover on further questioning that they had unwittingly continued in daily contact.

CONCLUSIONS

The title selected for this paper is "Some Causes of Failure." While I have endeavored to make my remarks inclusive particularly as to classification, I make no claim to completeness. I presume that I should conclude this paper by offering an outline of successive steps to be performed in the study and treatment of the resistant and obscure case. Unfortunately, however, allergy cannot be treated by rule of thumb. Every case must be treated on its individual merits and in accordance with its own peculiarities. The detective who works merely by the book, no matter how well written, will often fail to solve the difficult case. My plea is twofold, first bear in mind that greatest promise lies in finding the specific allergenic factor and, second, remember that whether this is found or not, you are treating not a disease but a patient with a disease, not asthma but an asthmatic.

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707 MEDICAL ARTS BLDG.

FURTHER OBSERVATIONS ON THE USE OF FILTERED AIR IN THE DIAGNOSIS AND TREATMENT OF ALLERGIC CONDITIONS*

BY MILTON B. COHEN, M.D., CLEVELAND, OHIO

AT THE meeting of the American Association for the Study of Allergy held in Washington, D.C., last May, I reported my observation on the effect of filtered pollen-free air on six patients with seasonal hay fever and asthma. These patients were treated in their own homes by means of electrically operated mechanical filters, which produced and maintained pollen-free air in their bedrooms. The filters consist of a motor driven suction fan covered by a filter bag made of several layers of a specially woven woolen cloth covered by one layer of cotton cloth, with the entire mechanism enclosed in a metal housing. The intake of the machine was connected to a special screen fitted to the window opening by means of a metal pipe (Fig. 1). As pollen-free air was forced into the room through the filter, a slight positive pressure was soon produced, and the old air rushed out through all the cracks and crevices. Thus it was unnecessary to seal the room or to change it in any way, and it became practical to treat patients by means of filtered air in their own homes. These filters remove 62 per cent of tobacco smoke with a particle size of 0.27 micron, and 95 per cent of zinc oxide with a particle size of 0.3-0.4 micron. They can be depended upon to remove all noncorrosive particles larger than one micron. It is readily seen that almost all dust particles are removed also and that by means of these filters it is possible to produce and maintain dust-free rooms. However, for experimental purposes it was desirable to have filters of even greater efficiency than these, and accordingly, machines were produced which were capable of delivering 250 cubic feet of air per minute of 99 plus per cent particle-free air.

With filters of the standard and the experimental type, studies were made to determine the following points:

1. Are there variations in the severity of hay fever and its accompanying asthma due to the dosage of pollen breathed in?

*From the Medical Service and the Allergy Clinic of Mt. Sinai Hospital.

Read before the American Association for the Study of Allergy, Minneapolis, Minn., June 12, 1928.

2. Will the breathing of pure, pollen-free air for a small number of hours daily suffice to keep the daily dose below the patient's threshold of reaction and maintain him free of symptoms, or will permanent residence in pollen-free air be necessary in (a) patients who have received no preseasonal pollen extract injections, and (b) in those who have failed to obtain complete relief by these means?

3. When symptoms are established and a patient is removed to an environment free from pollen, how long will it take for the acute symptoms to subside?

4. Can inhalant-free rooms be used to determine (a) whether symptoms are due to inhalant extrinsic causes and (b) as in the case of pollen, how long a period of residence in such a room is necessary for the control of symptoms, and (c) after the acute symptoms have subsided, how many hours' residence daily is required to prevent their recurrence?

For the study of pollen disease it was necessary only to install a filter in the patient's bedroom a few days before the beginning of the season of pollination of the plant to which he was sensitive, and to instruct him to sleep in this room. The usual occupation was continued, though golf, tennis, and auto rides were discouraged. As the season progressed, a report was made of the presence or absence of symptoms. Whenever the slightest symptoms arose, additional hours in filtered air were advised, until for each patient there was worked out a satisfactory schedule of time in filtered and in outside air. Quite early in these studies it was seen that the number of hours in filtered air necessary for any patient varied directly with the air pollen concentration. Eight hours usually sufficed for all patients during the first few days of the season. As the season advanced, more hours of residence were required, until the peak of the season, after which the requisite number of hours gradually diminished. For the mild patients, those who had previously been relieved by residence in average hay fever resorts or by a short course of preseasonal pollen antigen injections, from eight to twelve hours were sufficient. For the cases of moderate severity, from twelve to eighteen hours were required, and for the most severe ones, from eighteen to twenty-two hours were needed at the peak of the season to remain symptom-free. All patients who had received partial relief following preseasonal treatment were rendered symptom-free by a residence in filtered air for a few hours a day, usually not exceeding eight. In those patients in whom symptoms were well established, it required from two to seven days' residence in filtered air for the symptoms to subside. Their recurrence could be prevented by partial residence, as in those who began the use of filtered air before their symptoms began.

There are many asthmatics in whom it is extremely difficult to determine the etiology either by clinical experimentation alone or by skin tests followed by clinical experimentation. Usually, these are regarded as cases of bacterial asthma with its unsatisfactory treatment and poor prognosis. We have studied ten patients of this type, who have been placed in dust-free environments for periods of from seven to fourteen days. In creating a dust-free room the following procedures are followed: A bedroom of not exceeding 1500

cubic feet capacity is thoroughly cleaned, the walls are washed or repainted and repapered, all draperies and rugs, etc., are removed; the floors are oiled or waxed; all furniture is removed except a bed and a chair or two, which are thoroughly scrubbed: the mattress and pillows are covered with rubber sheeting or with Dupont's new satin fabricoid, which is to be preferred. If the home is heated by hot air, the furnace pipe must be hermetically sealed. A filter is then installed taking air from an adjoining room through the opening in the wall. The clean room is then held full of clean air under pressure, and no leakage from the rest of the house occurs. Five of these ten patients lost their asthma within a week, and all have remained asthma-free when similar environments have been produced at home and they have remained in dust-free air at home for from twelve to fifteen hours a day. This is in agreement with the reports of W. Storm van Leeuwen, who relieves a large percentage of all asthmatics by removing them to dust-free rooms. His apparatus is, however, extremely cumbersome and very expensive.

While it is realized that ten cases are not sufficient from which to draw any conclusions, it is obvious that about half of the patients in whom a diagnosis of bacterial allergy would have been made by exclusion, can be considered as inhalent asthmatics.

This report is presented in the hope that others may make similar studies so that more allergic patients may have adequate diagnosis and satisfactory relief.

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DISCUSSION

Dr. I. S. Kahn, San Antonio, Tex.—I think this work with filtered air is one of the valuable contributions we have had. I have been experimenting with pollen free rooms for probably three or four years, using first inside court rooms in a downtown hotel, then home-made filters, and then Dr. Cohen came out with this apparatus.

These pollen-free or pollen-reduced rooms have brought up some very interesting points with regard to etiology in bronchial asthma. I have had the same experience that Dr. Cohen has had, finding that there is a vast percentage of previously considered bacterial asthmas with negative pollen skin tests, which will clear up in such rooms.

When we had this discussion brought up in our meeting in Washington last year, Dr. Cohen had the idea that if the asthma case did not clear up in five days in a pollen-free room, it could not be a pollen case. I told him at that time he was wrong on that point, because I feel that it will take a considerable longer period of time before some cases will clear up. Hay fever cases clear promptly, but sick asthma cases who have taken adrenalin for years have so little resistance power, and do not seem able to get rid of this pollen toxin to a tolerance point within three or four days.

The last case I had behind a Cohen Filter took twelve days to clear. I have seen a filter require from one to two months in a sick asthma case before final clearing, and in one case in a pollen-free room, the longest I have ever seen, kept steadily in bed, took five months before it was absolutely clear—a sick adrenalin—exhausted individual.

I was glad to hear of the improvement in the Pollenair Company filter to get rid of the lint given off. I have put pollen plated out in the room behind the originally designed Cohen filter, and you would be surprised at the amount of hair particles trapped. Certainly some sick pollen cases are so annoyed by the lint and fuzz that comes off the machine that it prevents them from clearing up as they should. So simply because a case would not clear under the original Cohen filter, was not an indication that it was not a pollen case.

The apparatus Dr. Cohen has is a very pretty machine, and I find it very, very satisfactory. However, I have been using a home-made machine for three or four years

which is just as satisfactory, and any patient can build it for a few dollars. The machine I have works on the same principle except that I use an ordinary window screen and a backing stuffed with half the thickness of absorbent cotton such as comes in an ordinary pound roll, which is basted between cheesecloth, and an ordinary twelve or fourteen inch electric fan, and if necessary, two fans. The air currents from the electric fans will keep the pollen from coming in from the opposite direction or from the sides. In hot weather in Texas, we cannot use the patented filter because the room gets stuffy, smells, and I have to put in an additional electric fan or switch over to my homemade apparatus. I think any of you who are handling asthma cases are making a big mistake, both for diagnosis and therapeutic purposes, if you are not employing pollen filters of some kind in your work.

Dr. M. Murray Peshkin, New York City.—Dr. Cohen is to be complimented for encouraging the development and manufacture of the pollen filter. This machine has proved its efficacy by relieving patients with hay fever.

To my mind the pollen filter can also be employed for a purpose other than that it was originally intended. Patients whom are classed as environmental asthmatics and in whom all forms of specific and nonspecific therapy failed to give relief, have always been difficult to do anything for. In other words such a patient's tolerance for the particular environment is so low that appropriate therapy makes no impression on his regulartory mechanism. If he is removed from his environment, perhaps to the seashore or open country he frequently becomes entirely relieved from asthma. Upon returning to his former environment in spite of the fact that it has been rendered allergically proper, asthma recurs. The installation of an air filter in the bedroom of such a patient may be of extreme benefit.

Van Leeuwen has constructed a number of dust and miasma free chambers in which patients with asthma sleep. Some of these patients were able to go about their daily work, earning a livelihood, in extreme comfort while others were entirely relieved of asthma. The patients who were not greatly relieved were administered nonspecific treatment with extreme benefit. The cost of constructing these special chambers is very high and therefore beyond the reach of the average patient; whereas the installation of an air filter in a room properly prepared is comparatively inexpensive. The cost in fact is small when compared to the amount of money expended in an effort to obtain relief from the distressing symptoms of continuous asthma.

There is another type of patient with asthma who when removed to the public ward of a hospital, perhaps only a short distance from his home, becomes entirely free from symptoms within one to three days, and remains so during his entire stay in the hospital. This type of environmental asthma is obviously not expected to become free from asthma after the installation of an air filter in his home.

Dr. Milton B. Cohen, Cleveland, Ohio.—With regard to the question of stuffiness in these rooms, it not only happens in Texas but it happens in Cleveland or anywhere else. You get exactly the same temperature in the room inside as out when you have absolutely quiet air. All one needs to do in this circumstance is put a fan in the room to create a circulation of the air so the patient feels moving air, and then the room feels comfortable.

I did not refer to van Leeuwen's work because I did not want to take time on literature. He has two types of rooms. They are of the same type, but he ventilates them in two ways. He employs a metal room, 6x6x9, which is hermetically sealed and which is ventilated by means of an ordinary suction fan and a pipe taking air from the height of thirty or forty meters. He takes ordinary, plain outside air, unfiltered, and passes it through this small chamber which is absolutely free of dust. All he does in such cases is to remove house dust because he has built within his house a dust free place and he uses outside air. He does state there is a small percentage of asthmatics, three, four, or five per cent, in whom the ordinary outside air-borne things, he calls them miasms, produce trouble. In this type of case he has special clean air, not filtered, which he cleans by means of refrigeration. He claims if you freeze air, or bring it down to a low temperature where all the moisture comes out, it will bring out all the particulate matter and this air which remains

in the refrigeration apparatus is warmed and brought into the house, and it will be free of dust. He wrote me that the ordinary chamber cost $400 in Holland, and fom the pictures of the special installation, it looked as though it would cost $7000, $8000, or $10,000 to equip a house with such apparatus.

The filters which are being sold are the ordinary filters which will handle sixty-two per cent of tobacco smoke and all particles larger than half a micron. The filters which licked this lint problem can be obtained, but they are not generally on sale.

It is true that almost all patients, I will say 70 or 75 per cent, which you remove to a hospital environment, will clear up.

THE CONTRIBUTION OF AIR ANALYSIS TO THE STUDY OF ALLERGY*

Comparative Ragweed Records for Nine Large Cities

By O. C. Durham, Indianapolis, Ind.

CLINICAL records have long given evidence of great fluctuations in severity of symptoms experienced by hay-fever sufferers. These daily and seasonal variations have been difficult to understand and quite impossible to anticipate, though the factors that contribute to the situation have long been recognized in a general way. It is known that a particularly favorable growing season produces more luxuriant weeds and consequently abundant pollen, and that extreme weather conditions, such as a prolonged period of rain or very windy weather, have a direct effect on pollen distribution and hence upon the comfort of the hay-fever victims. The comparison of weather records with clinical records is of some help. But since the whole question seems to revolve around the point of the relative amount of pollen encountered day by day, the need of quantitative data has long been apparent. If one can feel certain of the numerical strength of his enemy he has already laid the groundwork of his defense. Certainly in a task which is *all* defense, the advantage of accurate statistics can hardly be overestimated.

The practical value of atmospheric pollen records depends on the simplicity of the technic and the scope of approximate accuracy of the results. The technic described below is certainly simple enough when one does not try to identify more than a few kinds of pollen. Since ragweed pollen is by far the most abundant in most parts of the country, it is possible for any careful technician to obtain reliable ragweed data the first season. The only real interference with the accuracy of the results is the large number of air borne soot particles encountered in some places. When this difficulty is encountered, a shelter should be arranged that will not interfere with the pollen counts. If this cannot be done, it will be necessary to make the exposures at some more favorable point.

There has been some question as to the practical value of results of counts made from a single station as it was thought that conditions even in

*Read before the American Association for the Study of Allergy, Minneapolis, Minn, June 11, 1928.

different parts of a city due to wind currents, wind direction, and the irregular distribution of vegetation would necessitate numerous counting stations to arrive at any accurate conclusion. In this we have been surprised greatly. Scheppegrell[1] found that pollen is encountered in fairly even concentration up to a height of a mile. Rowe[2] exposed plates at different levels of the eighteen story City Hall in Oakland and obtained practically the same counts at all levels. Koessler[3] and I found in Chicago that we got almost the same count on a given day from a tall building down town as from the ground in the suburbs. In fact, the daily results from five stations were quite similar. This was verified in a very striking way the past season by counts made independently by Duke[4] and myself in Kansas City, at points ten miles apart, the station of the former being 200 feet above the street in the heart of the business section and that of the latter in the suburbs. It is therefore feasible to conduct quantitative pollen studies, at least for the more abundant pollens, from one station in each center of population. The record obtained will represent the approximate condition over an area with a ten mile radius. Of course this will not apply to pollens whose source is localized or whose total output is small.

The need of comparative data from various parts of the country is becoming increasingly evident. During the last two years considerable effort has been made to interest allergy men in all parts of the country in this work, and as a result we are now able to add some interesting data to that already published and present a comparative ragweed study of nine cities in widely separated parts of the country. In several of these places only one survey has been made. For these great accuracy is not claimed, but their local and comparative value is still considerable. Particular mention is made of the courtesy of each local investigator in permitting us to use his data. Credit is given below.

TECHNIC

An ordinary microscope slide is coated with white vaseline and exposed face up in a chosen location for twenty-four hours. Under convenient low power the total number of pollen grains of the variety under investigation is then counted on a unit area and the average calculated for one square centimeter. Scheppegrell's[5] formulas are then used to calculate the average number of pollens per cubic yard of air for the twenty-four-hour period. It is not always practical to use the same power of magnification or the same unit area for counting, but tables and formulas are available[5] which permit of easy disposal of the calculations. For this survey "ragweed' includes pollen of all members of the ragweed family—Ambrosia trifida, Ambrosia aptera and some Iva ciliata, Iva xanthifolia, and Xanthium, and in California possibly some Franseria.

Materials.—Microscope with mechanical stage, plain glass slides, white vaseline.

Exposure.—Slides are coated with a thin even film of vaseline and exposed for twenty-four hours, face up in selected location with proper protection from direct wash of rain and fall of soot.

Counting.—For ragweed a low power field 1.4 mm. wide is used, and beginning at the edge of the slide, a count is made of all pollens encountered in crossing the slide (25.4 mm.). The slide is then shifted sidewise and another strip across it is counted. The total count for five such trips is the approximate number of ragweed pollens per cubic yard of air for the day under investigation. The width of the field can be calculated by a micrometer eyepiece and ruled slide or can be approximately calculated by means of the scale on the mechanical stage. The width of the field can be varied by lengthening or shortening the length of the microscope barrel. I use 120 mm. barrel length.

FLUCTUATION

Factors influencing the daily fluctuations in pollen content are, briefly, (1) humidity, (2) per cent of sunshine, and (3) wind velocity. Pollen is ripened in mature anthers early each morning. The process is interfered with if there is rain or excessive humidity. Sunshine is necessary at the ripening time, not only to complete the actual maturing of the pollen, but to reduce the moisture on the blossoms and in the air. Wind is all important as the distributing agent, and the greater the wind velocity, other factors being equal, the greater the concentration of pollen will be. It will be seen from the graphs that no factor or combination of factors has been sufficient to prevent distribution for a twenty-four-hour period after the season really begins.

COMPARISONS

The simplest items of information furnished by an air survey are the date of appearance of pollen in the air, the date of maximum distribution, and the length of the season. Ragweed pollen begins to appear on the plates in most localities early in August, but the average date of effective concentration seems to be about August 15. The length of the season is a matter of latitude,

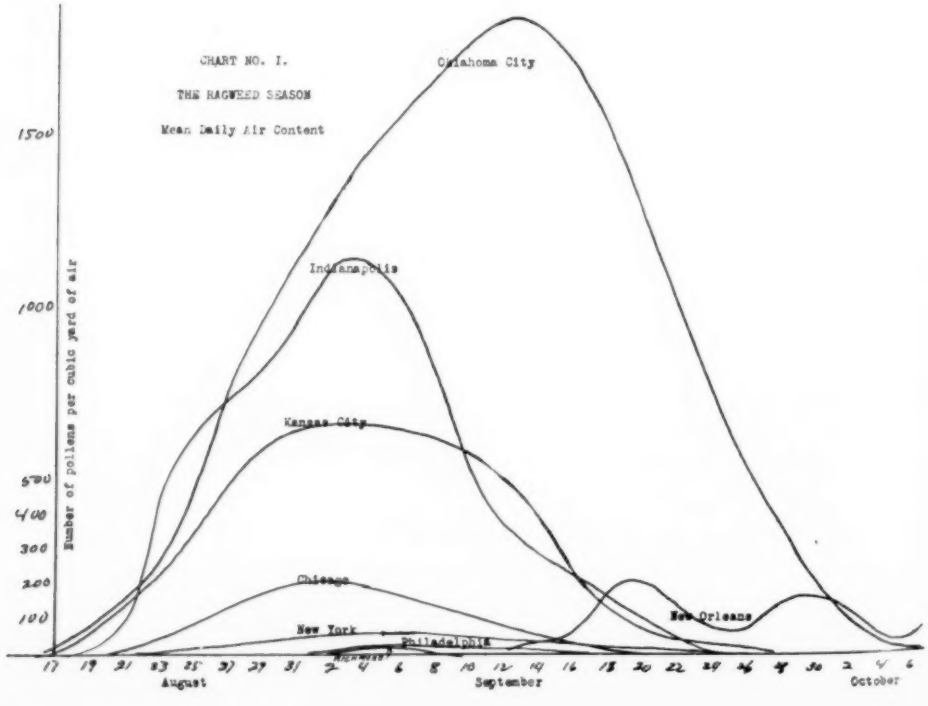
TABLE I

CITY	MAXIMUM CONCENTRATION	DAILY AVERAGE CONCENTRATION
Oklahoma City	3600 pollens per cu. yd.	814 pollens per cu. yd.
Indianapolis	2100 " " " "	470 " " " "
Kansas City	2237 " " " "	400 " " " "
Chicago	250 " " " "	100 " " " "
New Orleans	410 " " " "	75 " " " "
New York	100 " " " "	26 " " " "
Philadelphia	38 " " " "	10 " " " "
Richmond	12 " " " "	6 " " " "
Oakland	6 " " " "	1 " " " "
Average Midwestern City (Oklahoma City, Indianapolis, Kansas City)	2646 " " " "	561 " " " "
Average Eastern City (New York, Philadelphia, Richmond)	50 " " " "	14 " " " "

and where the season is long the date of maximum pollen counts is relatively later than where the season is short. In the northern cities the peak is found to come soon after September 1, in New Orleans late in September, and in California about October 10.

The greatest surprise encountered in studying the tabulated results of these nine surveys is the astonishing difference in maximum, average, and mean daily concentration in the different cities. These differences are so great that it is impossible to plot all the actual findings on the same scale. Maximum and average comparisons will be found in Table I. Comparison of average daily concentration is also shown in Chart II. Mean daily record is shown by smoothed curves in Chart I, and even thus it is impossible properly to represent New York, Philadelphia, Richmond, and California counts. In the latter part of this article all local records are drawn on suitable scales. We find the maximum concentration in Oklahoma City at the height of the season to be 300 times that of Richmond's highest count. For purposes of comparison, the figures for daily averages probably best represent the true conditions. The daily average concentration in Oklahoma is 136 times that of Richmond and the average daily concentration in the Midwest 40 times that of the East. It may then be said that with our present information the ragweed pollen incidence is 40 to 300 times as great in the midwestern cities as it is in the eastern cities.

Balyeat[6] has called attention to the fact that no differences in the weather factors entering into the production and distribution of ragweed pollen in these various places could possibly account for such extreme differences in air content, so we are forced to conclude that the amount of vegetation is the chief factor influencing the intensity of the ragweed season in various places. If these eastern records are typical, it seems fortunate that these centers of population are not exposed to the concentration of ragweed pollen that is encountered in the midwest. Since the three eastern records here included



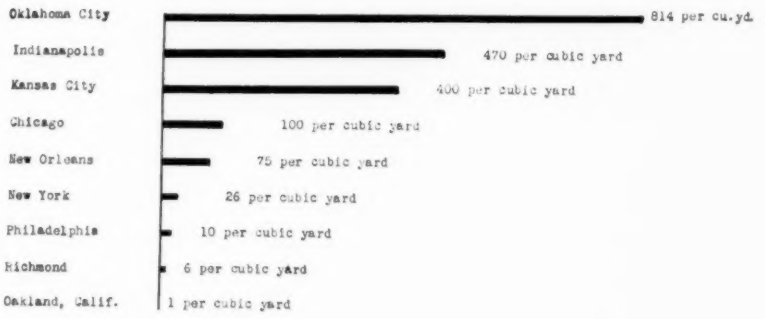
were all made during the same season by five careful technicians working independently but following identical technic, we are inclined to believe that they are representative of the true conditions. Whether there is actually a lower percentage of hay-fever sufferers in the East than in the Midwest is not known. We do know that the fall hay-fever symptoms are mild in Oakland, California, and with the report of Dr. Rowe, we seem to have reached the minimum toxic ragweed concentration.

In reading the charts accompanying the following surveys, it is very important to notice that it was necessary to use three different scales, none of which is the same as on Chart I.

CHART NO. II

COMPARISON OF DAILY AVERAGE RAGWEED

POLLEN CONCENTRATION



OKLAHOMA CITY, 1926-1927 (CHART III)

Records by Ray M. Balyeat, M.D.[6, 7]

The Oklahoma City records were made from plates exposed in the suburbs of the city. No doubt ideal weather conditions had considerable to do with the extremely high counts in 1926, but the really important factor was the unusually favorable spring and summer in that part of Oklahoma. The state enjoyed record cotton and corn crops—and record ragweed crop. Vegetation was not burned up in the summer, but frequent rains allowed it to reach its maximum development. Added to the favorable growing season all weather factors continued to be combined through the ripening season, causing unusually heavy distribution of the pollen. Scale is one-half that of Chart I.

INDIANAPOLIS, 1926 (CHART IV)

Record by Thurman B. Rice, M.D.[9]

Plates were placed on the roof of a downtown building (Merchants Bank Building) 300 feet above the ground. Some difficulty was encountered with smoke and soot, but it is interesting to study data made in the heart of a city of 350,000 people. The fluctuations of the curve are more regular than on any other chart yet encountered. Same scale as Oklahoma City.

KANSAS CITY, 1926-1927 (CHART V)

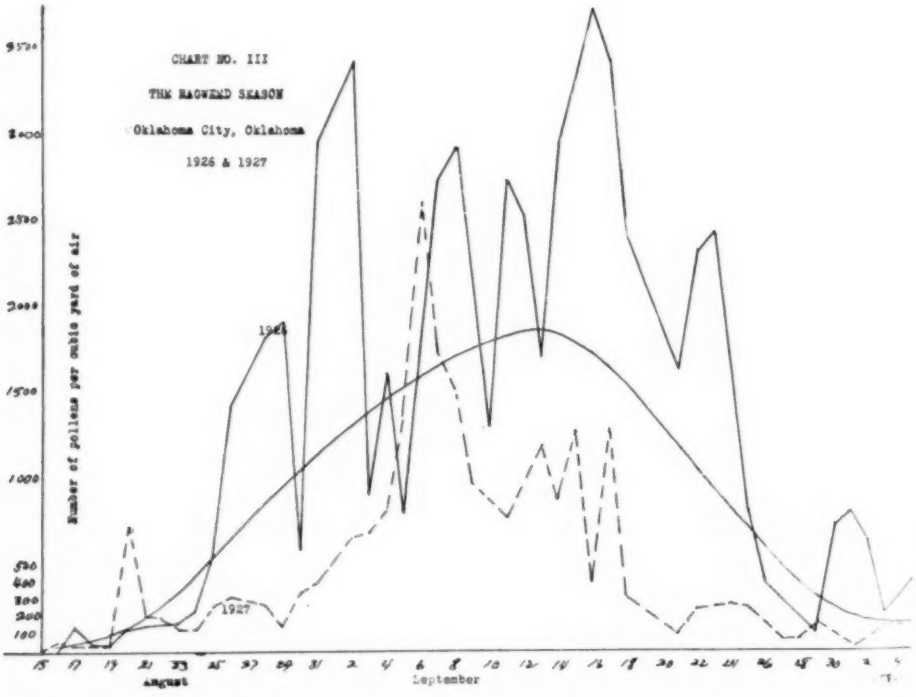
Records by O. C. Durham

The plates were exposed in the extreme southeast part of the city. The appearance of the 1926 curve is affected most by the two days of greatest pollen incidence coming not in the middle of the season, but two weeks apart. It is evident that our conclusions are much more accurate in these cities where we have data for two seasons. Same scale as above.

CHICAGO, 1925 (CHART VI)

Record by K. K. Koessler, M.D.[3]

In this survey the data came from an average of four stations. The stations were established at widely separated points, the situations representing the utmost variation in actual conditions under which pollen is encountered



in the city. We felt that weather conditions were especially unfavorable, but without subsequent data we are unable to say how nearly the record represents the average condition of Chicago. As stated before, we did find that the daily concentration was practically the same at all stations. Scale same as above.

NEW ORLEANS, 1916-1918-1922 (CHART VII)

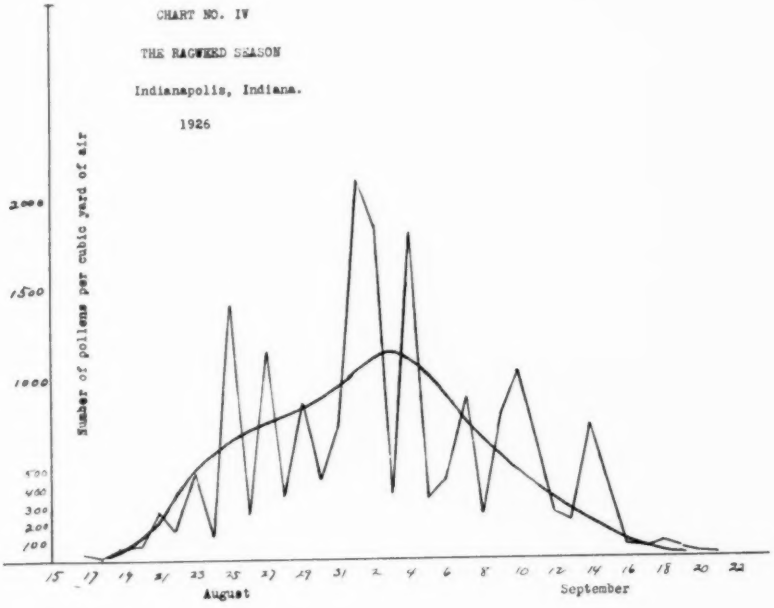
Record by Wm. Scheppegrell, M.D.[5, 8]

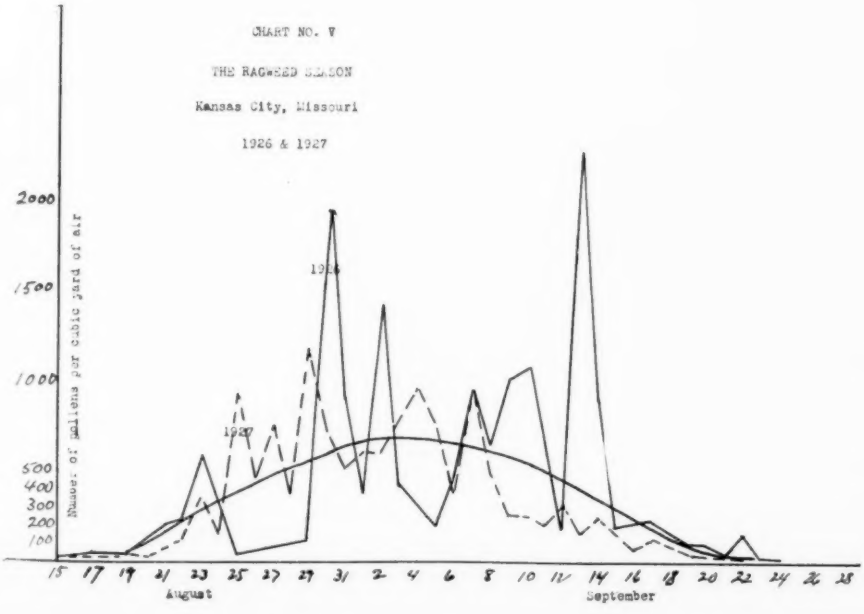
The average pollen concentration of New Orleans is comparable to that of Chicago. The length of the season and the late climax compared with northern cities is interesting. Note change of scale, 4 times that of Chart I.

NEW YORK CITY, 1927 (CHART VIII)

Record by M. M. Peshkin, M.D.[10]

Plates were exposed at 562 West End Ave. It would seem that the pollen situation on Manhattan Island is not very serious, and if it were not for the succeeding surveys we would be inclined to think that there had been some mistake in the calculations. However, these have been checked and rechecked





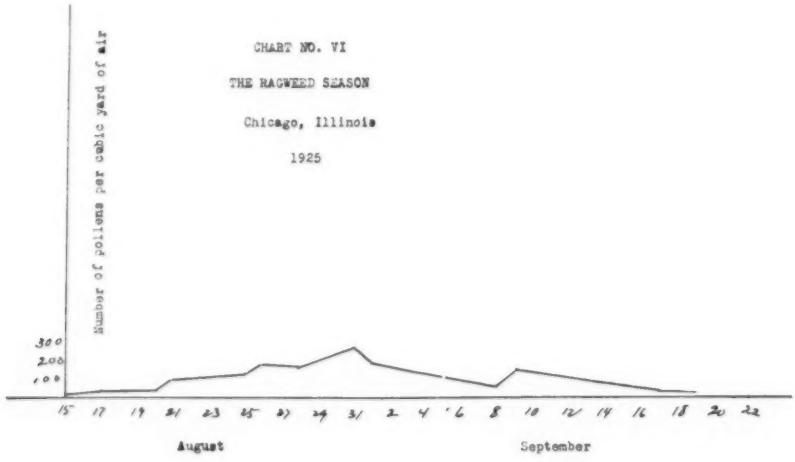
and after granting a most liberal factor for error the results are remarkably small compared with our midwestern statistics. Scale 20 times that of Chart I.

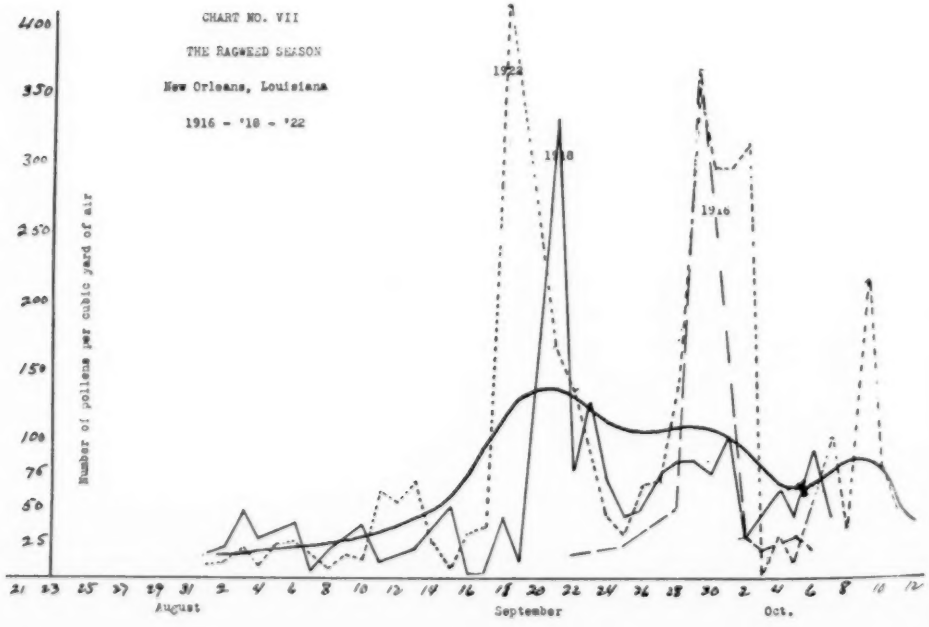
PHILADELPHIA, 1927 (CHART VIII)

(Two Independent Records)

By J. Alexander Clarke, M.D.,[11] and H. B. Wilmer, M.D.[12]

Dr. Clarke's plates were exposed at Swarthmore, a suburban town ten miles west of Philadelphia. Dr. Clarke feels that the season was milder than usual. Dr. Wilmer conducted two surveys, one in Philadelphia and one in the suburb of Germantown. Data for the former was obtained at the Pres-



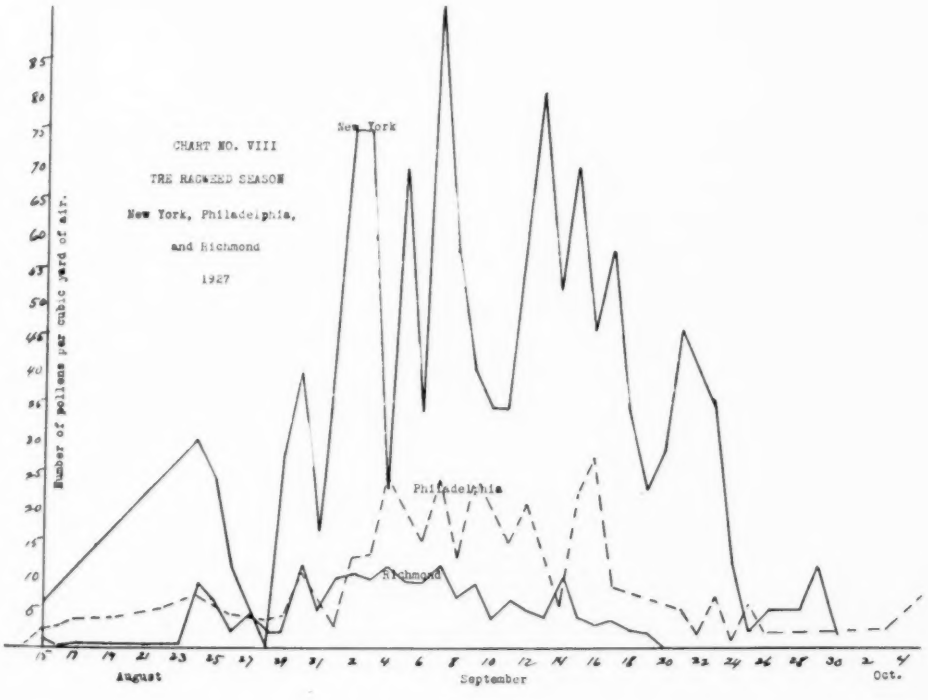


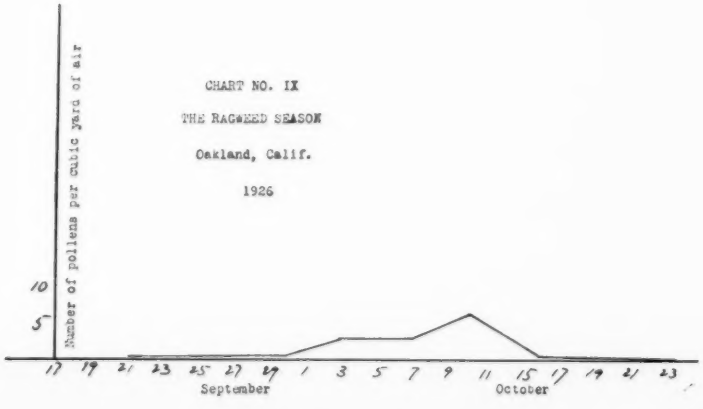
byterian Hospital by Dr. Herbert M. Cobe, and for the latter by Dr. C. A. Whitcomb. The graph on Chart VIII is the average of the Swathmore and Presbyterian Hospital counts, which were quite similar and both higher than that of Germantown. Thus of the three eastern cities studied in 1927, we have for Philadelphia the most accurate record.

RICHMOND, VA., 1927 (CHART VIII)

Record by Warren T. Vaughan, M.D.[13]

For this record plates were exposed on the seventh floor of an office building in the center of the city and in the edge of the city. As similar daily





counts resulted, the suburban plates were discontinued. While the counts are very low, the curve is typical and consistent with that of the other eastern cities.

OAKLAND, CALIFORNIA, 1926 (CHART IX)

Record by Albert H. Rowe, M.D.[2]

Dr. Rowe has made the most thorough atmospheric survey yet reported. It is one of the only two surveys that cover the entire pollen season, which in this case is the whole year. The ragweed figures are incidental in the report, as there is so little ragweed in the vicinity of Oakland, but it is here included to make this article complete for all published ragweed data and because it furnishes a real minimum for comparisons. Scale of graph the same as for the eastern cities on Chart VIII.

CONCLUSIONS

1. Daily atmospheric pollen records afford practical quantitative data useful locally in planning hay-fever treatment.

2. Average ragweed pollen incidence is markedly higher in the Midwest than in the East.

3. There is practically no ragweed pollen in the air in California.

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[11]Unpublished data.
[12]Unpublished data.
[13]Unpublished data.

CARE OF SWAN MYERS CO.

LABORATORY METHODS

THE NONSPECIFIC DIAGNOSIS OF ALLERGIC DISEASE: FURTHER OBSERVATIONS*

By Samuel M. Feinberg, M.D., Chicago

THE high degree of specificity prevailing in the allergic individual has been perhaps the earliest and most constant observation made with respect to human hypersensitiveness. It has been repeatedly noted and accepted as a basic fact that when one is hypertensive to a particular atopen an allergic reaction cannot be produced by exposure to another atopen. Similarly, the cutaneous reactivity will show a corresponding specificity. There may be considerable argument as to the theoretic explanation for this specific response, whether it is a specific ferment action or whether it is another type of antigen-antibody reaction, or whether it is explainable by some other form of biologic imbalance. But there is hardly anyone who is not firmly convinced of the strictly specific nature of this phenomenon.

The conception that all allergic individuals might show a reactivity to one and the same protein would be contrary perhaps to most of the prevailing theories in regard to the mechanism of allergic reaction. However, it has been found that there is at least one substance which is capable of giving a cutaneous reaction in allergic individuals, to which practically all allergics show a definite skin reaction and nonallergics do not. Whether these are instances of general hypersensitiveness to this substance is rather doubtful: it may mean perhaps only a phenomenon of the dermal tissues.

In a previous communication[1] we have called attention to the fact that when 0.02 c.c. of an extract of human dander is injected intradermally in an allergic asthmatic a typical urticarial reaction results, whereas in nonallergics this test is negative. At that time we gave a tabulated report of 20 asthmatics who were sensitive to proteins as shown by the cutaneous tests; the human dander test was positive in all. In a small group of asthmatics who showed no positive skin tests the dander test was negative.

Van Leeuwen,[2] in 1922, originally described this reaction and stated further that it is applicable to all forms of allergy. Later[3] he found that some of these extracts also give positive reactions in normal individuals. Such preparations must be discarded or purified by filtration through collodion membrane. In 1926[4] he estimated that this test is positive in 90 to 95 per cent of all allergics and never in normals. As an explanation of this phenomenon he offers the suggestion that the substance present in dander causing this reaction may be the same substance present in house dust, and that it may come

*Read before the American Association for the Study of Allergy, Minneapolis, Minn., June 11, 1928.

from the latter getting into the scalp. Van Leeuwen believes that the reactive material is composed of animal and plant parasites, particularly Aspergillus fumigatus.[5] He further suggests that reactions to animal hair or dander may be due to the same causative factor.

Keller[6] reports that the van Leeuwen test was positive in all of a series of 21 cases of the type of eczema which he terms "spätexudatives Ekzematoid." He also mentions the fact that out of 2 cases of hay fever, one showed a positive reaction, and in 2 cases of urticaria the test was negative.

METHOD

It is my purpose in this communication to report the results of this reaction as carried out on a greater number and variety of cases. The material was prepared in the following manner: To 1 gram of fresh human dander was added 100 c.c. of physiologic salt solution and allowed to stand twenty-four hours. The filtered solution was then sterilized by Berkefeld filtration, tested for sterility, and sufficient phenol for a final concentration of 0.5 per cent added. Before any batch of extract was accepted for use it was necessary to obtain a positive reaction in several previously proved allergic individuals and to show an absence of reaction in a number of nonallergics. I have found it more suitable to use 0.02 c.c. of the extract instead of 0.05 c.c. as suggested by van Leeuwen. This amount is injected intradermally on the forearm, using a control injection of phenolized salt solution on the opposite arm. A positive reaction consists of a definite urticarial wheal with surrounding erythema and usually associated with itching. This occurs usually in five to ten minutes.

RESULTS IN BRONCHIAL ASTHMA

The cases reported here include those reported in our previous communication. All of the cases reported in this paper were completely tested with the usual protein tests by the cutaneous method. The results are summarized in Table I.

TABLE I

	NO. OF CASES	VAN LEEUWEN TEST	
		POSITIVE	NEGATIVE
Asthma	134		
Total sensitive cases	94	94	0
Sensitive to proteins other than house dust	72	72	0
Sensitive to house dust only	19	19	0
Sensitive to foods only	3	3	0
Slightly positive to house dust	2	0	2
Negative to all proteins, including house dust	40	0	40
Hay Fever, total	38		
Uncomplicated	21	17	2 (2 sl't pos.)
Complicated by other allergic disease	17	17	0
Hyperesthetic Rhinitis, total	11		
Sensitive to proteins	6	6	0
Negative to proteins	5	5	0

In a series of 134 cases of asthma in which both the complete cutaneous tests with all proteins as well as the van Leeuwen test were made the following results were obtained. In 94 cases of this series, or 70 per cent, positive tests were obtained to various proteins, of which 19, or 14.1 per cent, showed house dust as the only causative factor, and 3 showed foods as the only reacting agents. The van Leeuwen reaction was positive in this entire group of protein-sensitive cases. It is interesting to note in this connection that even those cases which did not show specific reactions to the individual proteins but gave a strong reaction to house dust only showed a positive van Leeuwen test in every instance.

In this same group of 134 cases there were 40 patients in whom the van Leeuwen test was negative. This group consisted of typical bronchial asthmatics, asthmatic bronchitis, and two or three other varieties of dyspnea. In all of these complete protein skin tests were made and found to be negative. The house dust extract was found to be negative also with the exception of two weakly positive reactions. In conjunction with these experiments from time to time control tests were carried out on normal individuals or those suffering from unrelated illness. These showed negative results.

HAY FEVER

It is regrettable that I had paid little attention to this reaction in hay fever cases in past seasons. Part of this neglect is attributable to the fact that I had considered it unimportant to investigate this phase of the van Leeuwen test, as hay fever patients are known to react to proteins almost invariably and, therefore, the practical value of such a test was not apparent. However, it now appears that the van Leeuwen reaction may possibly have another significance, and for this season, therefore, I have thought it worth while to try this reaction on the hay fever patients.

To date I have investigated the reaction of human dander extract in 38 cases of hay fever. Of these cases, 21 were uncomplicated by any other form of allergic disease; positive van Leeuwen tests were obtained in 17, weakly positive in 2, and negative in 2. One of the negative reactions was in a patient who had had three years of adequate treatment and who gave a negligible reaction to pollens this season. One of those giving a weakly positive van Leeuwen test also showed weak reactions to pollens. In the other 17 cases the hay fever was complicated by other allergic disease such as bronchial asthma, hyperesthetic rhinitis, or urticaria; the van Leeuwen test was positive in all of these. As a whole, the reactions in the hay fever cases were not as strongly positive as in the asthmatics.

HYPERESTHETIC RHINITIS

In a series of 11 cases of hyperesthetic rhinitis, uncomplicated by any other allergic disease, in whom complete protein tests were made, including the van Leeuwen test, the following results were obtained. In 6, positive skin tests were obtained to some proteins, two of which were sensitive to house dust only. All of these proved allergic cases gave a positive van Leeuwen reaction. In the 5 who gave no skin reaction to any protein, the van Leeuwen test was negative.

URTICARIA, ECZEMA, ETC.

At this time I am unable to present any report on any series of cases of urticaria or eczema in which complete skin tests were checked up with the van Leeuwen reaction. From the occasional case in which I have had the opportunity to do this my impression is that the human dander extract reaction goes hand in hand with the specific protein reaction; i.e., if there is any cutaneous reaction with any protein there will also result a positive van Leeuwen test. However, it would require more extended observations to give a decided opinion on this phase of the subject.

It would seem logical to attempt to investigate this reaction further in such conditions which are claimed by some to be of allergic origin, such as migraine, angioneurotic edema, some forms of arthritis, and others. This is now under process of investigation.

HAIR EXTRACT

In order to determine whether this reacting substance is present in greater concentration in the dander or the hair, fluidextracts of human hair were prepared by a similar technic as that used for dander. On several patients comparative tests were made with the dander and hair extracts. Although occasionally a patient gave a strongly positive reaction to the hair extract, most reactions were very weak or entirely negative.

It is also worthy of note that in almost every instance in which the van Leeuwen test was positive and in which I have tried the intradermal house dust extract, the latter was also positive. However, very many of these house dust reactions were not as strikingly positive as those produced by the dander. Nevertheless, it is possible that we have also in house dust the same or similar substance that is present in human dander and which is responsible for the skin reaction.

DISCUSSION

The results obtained in the foregoing experiments would indicate that the intradermal test with extract of human dander is a valuable means of determining the patient's reactivity to protein substances. Whether or not it can be of use in allergic individuals who do give specific cutaneous reactions has not been settled. It is unquestionably, therefore, a great diagnostic aid.

An attempt to explain this reaction on the basis of our conception of hypersensitiveness suggests several possibilities. It may be argued that these cases which react to human dander extract have become hypersensitive to human epithelium. This, of course, is not in agreement with our clinical observations. Another possible explanation is that the individual has become hypersensitive to a specific substance which attaches itself to the epithelium. Van Leeuwen thinks that this substance is the allergen of fungi, particularly Aspergillus fumigatus. It would be difficult to explain, however, how all allergic patients can become specifically hypersensitive to the same protein.

The contention that this reaction may be due to the presence of toxic split-protein products is open to argument because we would also expect a similar reaction in nonallergics. However, the possibility that the variation

between allergics and nonallergics may be only a quantitative difference has not been investigated and may perhaps not be contrary to our split-protein theory. In substantiation of this it has been recently shown[7] that the human skin when extracted with alcohol contains a substance that flushes and wheals the human skin when punctured into it, and that the epidermis contains this substance in greater concentration than the dermis.

SUMMARY

1. An extract prepared from human dander and injected intradermally shows a positive skin reaction in practically all individuals manifesting cutaneous reactivity to proteins.

2. In a series of 183 cases of bronchial asthma, hay fever, and hyperesthetic rhinitis, in which complete protein skin tests were made, with positive results in 138 and negative in 45, the human dander test failed to show agreement in only 4 instances.

3. It is suggested that there may be a valuable diagnostic feature to this reaction, not only in the conditions described, but perhaps also in other manifestations in which the etiology of allergy is still in debate.

4. It is possible that there may be found other materials containing substances capable of giving a similar reaction.

5. The occurrence of such a reaction in all allergic individuals without regard to the specific protein to which the individuals are hypersensitive would tend perhaps to invoke a modification of some of our conceptions regarding specificity in hypersensitiveness.

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DISCUSSION

Dr. M. Murray Peshkin, New York City.—Two years ago I tested fifty children with allergic asthma to an extract of human dander and another fifty children with Aspergillus fumigatus. The intradermal and scratch tests were performed in every case. These preparations were kindly furnished by Dr. Van Leeuwen of Leiden, Holland. I can state now that in only a few instances were positive reactions obtained with either of these preparations.

The following experience will be of interest to note. One and one-half years ago a female patient, a manicurist by occupation, came under my observation for bronchial asthma. Her attacks of asthma were always aggravated and frequently induced on the days when much hair clipping was performed in the barber shop where she was employed. She showed strongly positive scratch reactions to both the fluid and powdered extracts of human hair and dander. Positive reactions were also obtained to a number of other protein substances. A subcutaneous injection of 0.1 c.c. of a 1-10,000 dilution of human

dander caused a violent local reaction persisting for several days. I felt justified in assuming that I was now dealing with a definitely potent extract of human dander. With this extract over 100 patients with asthma were tested intradermally and positive reactions were obtained in only a few instances.

In a patient with asthma exhibiting multiple positive protein skin reactions the problem for the investigator is to determine which protein or proteins are the existing etiologic factors. If this is not accomplished then from a practical standpoint the knowledge that the patient is allergically sensitive is of no value. The knowledge that such a patient also reacted to human dander would likewise be of no practical value. However, if we had at our disposal a single remedy, perhaps a complex synthetic chemical which when injected into an allergic asthmatic would alter the reactivity of the host in such a manner as to render him from symptoms in spite of exposure to a known exciting factor of asthma, then any single test that will enable one to make a positive diagnosis of allergy would be of unquestionable value. Such a test, however, must pass all suspicion of not being nonspecific in nature and must not give pseudoreactions. In the light of my experience I cannot accept, at this time, the van Leeuwen test as a specifically diagnostic test for allergy.

Dr. Ray M. Balyeat, Oklahoma City, Okla.—Last fall about the first of October we began intradermal testing with human dander made up as Dr. Feinberg makes his and I must say that our experiences differs very materially from Dr. Peshkin's, and conforms largely with the experience of Dr. Feinberg. We have run a series of something over 250 in which we found that in those patients who are having migraine or urticaria that the reaction to human dander is seldom positive, while in the majority of cases who are sensitive to pollen only very mild reactions to human dander occur, but in practically all cases who are very sensitive to animal dander the human dander is very strongly positive.

In the collecting of human dander it is very interesting to note that it is not easily obtained, although we frequently think of human dander as being very prolific. However, it does not seem so when the actual collecting is taking place. I might say, in regard to our collecting, that it is obtained from the heads of our insane people, and that it can be obtained, as a rule, in large quantities from patients suffering from encephalitis lethargica.

Now in regard to its practical value, I think it is going to be of some value. For example, two or three patients came into the office and after taking the history I thought that they were entirely hypertension cases suffering from cardiac decompensation with asthmatic symptoms, simulating true asthma. On testing them first with human dander we found them strongly positive, which led us to go further with our tests, and they proved to be true asthmatic cases complicated with hypertension. It seems to me that if one finds patients strongly positive to human dander that we are justified in searching very carefully for an allergic factor as a cause.

Dr. Leon Unger, Chicago, Ill.—Dr. Feinberg and I are associated with the Northwestern Clinic, and we do very complete skin testing, running through 200 to 250 tests on each case. We have been running both the allergic, and the cases we deem nonallergic through the same routine of skin tests.

The value of the van Leeuwen test seems to lie in the elimination of the necessity of skin testing in the nonallergic group of cases. We have found without exception, as Dr. Feinberg has pointed out, that every single case that has had negative skin tests has been negative to the van Leeuwen test. This group includes cardiacs and so-called asthmatic bronchitis and other patients.

We have also found, as Dr. Feinberg pointed out, that practically every single case of allergic patients with one or two exceptions has been positive to the Van Leeuwen test.

I know Dr. Feinberg has been very conscientious in this work and he has discarded several batches of material. If he gets a batch and tests it out on normals and finds that the normals give positive, he immediately discards the batch of material and runs some more. If he finds that the allergic cases give negative reaction, he discards the batch and prepares fresh ones, as he explained. Then when he gets a batch which gives negative skin

tests on normal individuals, students and nurses, and so forth, and gets a batch which gives positive reactions to allergic cases, those who give positive skin tests, then that is the batch we use for testing for the patients.

Our results at the clinic have been very gratifying, and I cannot understand why Dr. Peshkin has not obtained satisfactory findings. I am sure that the work will go on and at the next meeting Dr. Feinberg will probably have more to report on this subject. In the meantime, the test offers us a tremendous help in eliminating the necessity of skin testing the nonallergic group of cases. If we find a heart case or a hypertension case, we immediately do a van Leeuwen test. If the test is negative as it practically always is, we know these patients are nonallergic, and we don't have to run through 200 or 250 skin tests which our experience has shown always prove negative in is particular group of cases. Up to the present time we have been testing these cases thoroughly, but we are contemplating dropping the skin tests in those patients who give negative von Leeuwen tests.

Dr. Samuel M. Feinberg, Chicago, Ill.—I have tried to convey the impression that this particular reaction is positive in individuals that give reactions to other proteins. I did not mean to convey the impression that if it is negative the asthma is nonallergic, as a patient may still be allergic and not react to proteins. Apparently, these do not react to the van Leeuwen tests. In other words, the same influence affects the skin, which apparently influences it to reactivity to the van Leeuwen test; thus my series of cases really is a comparison of the specific cutaneous tests to this intradermal human dander.

I do not know why Dr. Peshkin has not been able to corroborate this work. There are possible explanations for his failure. That particular specimen which he got from van Leeuwen may have been old. I have found very frequently when I have had an extract for two months it fails to work or fails to react very much. I have made it my practice to make a new batch at least every month. That is one thing.

Another thing is that he is dealing, as I understand it, almost exclusively with children, and we know children do not give the same or equal cutaneous response that adults do ordinarily. Positive cutaneous responses in children are frequently of a degree that we would call negative in adults. Still, we can say they are of significance in children. It may be the interpretation in children is something different from that of adults as far as the positivity of a test is concerned.

As to the practical value of the test, Dr. Peshkin again fails to see its importance. I think that that point has been covered by Dr. Unger in his discussion: that when I get a negative test, in my estimation at least, I am quite certain that I am going to fail to get any specific cutaneous reactions. I have not failed to make the individual protein tests in all of these cases nevertheless for the sake of control and experiment. Every time I get a new patient, whether it is hyperesthetic rhinitis or asthma, if I have the proper extract, I make an intracutaneous test, and if it proves negative I very often tell the doctor or the patient I do not think it advisable to go ahead with the tests. If the doctor wishes it, that is all right. If the patient insists that is another matter.

Invariably I have found I could foretell negative skin reactions. I have not had the opportunity to test out any possible allergics who do not give cutaneous reactions. Whether this test would react on them or not I am not sure.

I am glad to hear that Dr. Balyeat has in a great measure corroborated my findings.

DEPARTMENT OF REVIEWS AND ABSTRACTS

ROBERT A. KILDUFFE, M.D., ABSTRACT EDITOR

CLINICAL AND EXPERIMENTAL

BONE CYST: The Etiology of Solitary Bone Cyst, Phemister, D. B., and Gordon, J. E. Jour. Am. Med. Assn., October 30, 1926, lxxxvii, 1429.

The clinical picture of this case was definitely that of an infectious disease. However, the gross and microscopic pictures of the lesion in the humerous were practically typical of a bone cyst. The very large number of giant cells producing extensive areas in the lining membrane that were almost identical with benign giant cell tumor gave the tissue an aspect that was markedly different from that seen in ordinary pyogenic osteomyelitis. At the same time, there were leucocytes in sufficient numbers to characterize it as inflammatory. The tibial lesions also contained large numbers of giant cells, but there the leucocytic infiltration and exudation were much more extensive.

The microscopic picture simulating giant-cell tumor suggests a possible inflammatory nature for that disease and the possibility that bone cyst in childhood is from the same cause as benign giant-cell tumor, which occurs almost entirely in adults. Cases are seen in late adolescence or early adult life, in which it is difficult to say whether the lesion should be classified as bone cyst with a thick fleshy lining or benign giant cell tumor which has undergone cystic degeneration. Benign giant-cell tumor has often been regarded as a chronic inflammation, but as yet there is no bacteriologic evidence to substantiate the view.

The evidence in these two cases is too incomplete to be conclusive, but it is strongly suggestive that Streptococcus viridans, isolated in each instance from the bone cyst, was the cause of the disease. Animal experiments were insufficient in one case and unsuccessful in another. The fact that the microorganism is the same as that found by Gilmer and Moody, Rosenow, Haden and others in chronic periapical dental infections, which usually develop silently, producing extensive bone absorption and frequently large pockets without surrounding new bone formation, lends support to this view.

TUBERCULOSIS: A Comparison of the Pirquet, Mantoux, Ring, and Tubercumet Tests in Lymanhurst Children, Stewart, C. A., and Collins, A. E. Am. Jour. Dis. Child., September, 1926, xxxii, 367.

In healthy children having negative tuberculin tests, the ring and tubercumet tests are uniformly negative.

In children not suffering from acute infections, but having positive Pirquet and Mantoux tests, together with such clinical findings as enlargement and calcification of the bronchial lymph nodes, slight occasional elevation in temperature, undernutrition and a history of exposure to tuberculosis but with no evidence of clinically active tuberculosis, the ring and tubercumet tests are negative. Under such circumstances, negative ring and tubercumet tests apparently are confirmatory evidence that the tuberculous focus is inactive and thus of definite clinical value.

In definitely active tuberculosis the ring and tubercumet tests usually are positive.

Positive ring and tubercumet tests are not specific tests for active tuberculosis, for they may become temporarily positive as the result of acute nontuberculous infections.

To be of significance, the positive ring and tubercumet tests should be persistently positive. Under such circumstances when certain chronic nontuberculous infections, such as pyelocystitis, osteomyelitis, and others are excluded, persistently positive ring and tubercumet tests should cause one to suspect strongly the presence of active tuberculosis.

A diagnosis of active tuberculosis on the basis of positive ring and tubercumet tests alone should not be made.

In making a diagnosis of active tuberculosis, the results of the ring and tuberculmet tests should be used with and not to the exclusion of other established methods of examination.

Tests, such as the ring and tuberculmet reactions, which are known to be positive in cases of active tuberculosis and negative in healed tuberculosis, undoubtedly will prove of value when their limitations are fully understood.

The Intracutaneous Salt-Solution Wheal Test, Stern, W. G., and Cohen, M. B. Jour. Am. Med. Assn., October 23, 1926, lxxxvii, 1355.

In the absence of edema, the intracutaneous salt-solution test is a simple, rapid, and accurate method of determining circulatory deficiencies in the extremities.

Sixty minutes or more is the normal disappearance time of the salt solution.

In all instances in which clinical circulatory deficiency exists, the disappearance time is diminished; in the area just above the seat of gangrene (existing or threatened), it is frequently as low as five minutes.

REVIEWS

Books for Review should be sent to Dr. Warren T. Vaughan, Medical Arts Building, Richmond, Va.

Works on Allergy

UNFORTUNATELY the major portion of the available contributions on allergy both experimental and clinical are widely scattered through a large number of current periodicals. The student of this subject is therefore faced at the outset with considerable difficulty in the building up of his reference library. At the same time there are many excellent monographic contributions which as a whole make a very good three foot reference shelf.

Many of the earlier works dealing especially with fundamental principles are long since out of print and therefore need not be mentioned. Two of these however are certainly deserving of a few remarks. Blackley's original book written in 1873 is an inspiration to all who have an opportunity to read it. In his *Experimental Researches on the Causes and Nature of Catarrhus Aestivus Hay Fever or Hay Asthma* we find that he has anticipated most of the methods which we employ today. In this book we find a method for pollen plating and counting very much as we use it today and a pollen prevalence curve which is directly comparable to the many which have appeared within the last few years.

The other of the out of print works which should receive especial mention is Vaughan's *Protein Split Products in Relation to Immunity and Disease* for in the reviewer's opinion an acquaintance with the contents of this book and the viewpoint of the author gives the reader a clearer understanding of the fundamental processes of anaphylaxis and allergy than does any other of the older works. It is true that newer theories have since been proposed, the terminology of which conforms more to the more recent knowledge gained particularly from a study of colloidal chemistry but so far no new basic theory has received generalized recognition or supplanted the older theories summarized in this work.

Among the works on clinical allergy Duke's *Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy* and Scheppegrell's *Hay Fever and Asthma* should still find a prominent place on the book shelf of every allergist. Duke finds allergy a factor in a remarkable diversity of clinical conditions. Since the appearance of his book nearly all of these observations have been confirmed by other workers. This is the only work in which any great amount of attention has been given to Physical Allergy.

Scheppegrell deals almost entirely with pollen allergy. The reviewer feels that his book should be widely read particularly because the botany of allergy is more comprehensively given than in any other monograph.

On the other hand since this work was published the list of hay fever producing plants has received many additions and some revision. The second edition of Balyeat's *Hay Fever and Asthma* contains a large section devoted to botany and is the only work in which the list of hay fever producing plants is entirely up-to-date.

Balyeat's book was written primarily as a manual for the use of the patient and can be highly recommended as such but at the same time it is a book that may be read with profit by the physician and indeed by the allergist.

Another 1928 addition to the allergy shelf is Thomas' *Asthma*. It contains minutiae which are of service to the beginner but its chief value to the student of allergy lies in the

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NOTE: In so far as practicable the book review section will present to the reader (a) interesting knowledge on the subject under discussion, culled from the volume reviewed, and (b) description of the contents so that the reader may judge as to his personal need for the volume.

We trust that the scientific information printed in these pages will make the reading thereof desirable per se and will thereby justify the space allotted thereto.

author's detail of his methods for bacteriologic study and treatment. For Thomas is one of the group who are confident that specific bacterial sensitization plays a part in asthma.

Two volumes which are always desirable as reference works and between the covers of which a wealth of information is contained are Kolmer's *Infection, Immunity and Biologic Therapy* which has a large section devoted to clinical allergy and Zinsser's *Infection and Resistance*. Another much smaller volume which should find a place and which has likewise already been reviewed in these columns is Wells' *Chemical Aspects of Immunity*.

We can say quite truthfully that the outstanding recent advances in the study and treatment of clinical allergy have been made in this country. We do say also with some degree of truth that interest in the subject in Great Britain and on the Continent has lagged far behind American interest. But there are certain important exceptions. In France interest in anaphylaxis has never lagged. True, until recently at least, skin testing has not been prosecuted as vigorously as on this side of the Atlantic but there are few phases of anaphylaxis and allergy in which the contributions of French authors will not receive considerable mention.

Charles Richet who in 1902 coined the word anaphylaxis published in 1923 a fairly complete review of work that has been done in the intervening twenty years and brings his conceptions of anaphylaxis up-to-date. Little mention is made of clinical allergic manifestations, his interest being primarily in experimental anaphylaxis but this in no way detracts from its interest to the allergist.

Among other relatively recent French contributions well worthy of possession are Lumière's *The Problem of Anaphylaxis* in which he presents his theory of colloidal precipitation; Arthus' *From Anaphylaxis to Immunity;* Danysz' *Theory of Immunity, Anaphylaxis and Antianaphylaxis;* Minet and Leclereq's *The Practical Applications of Anaphylaxis*, in which the authors discuss such conditions as serum sickness, drug idiosynerasy, echinococcus sensitization, anaphylaxis in infectious diseases, diagnosis of cancer, of echinococcus infection, of typhoid fever and tuberculosis, and anaphylaxis in general; Laroche, Richet and Saint-Girons' *Alimentary Anaphylaxis*, primarily a clinical study; and Galup and Segard's *Pathogenesis and Treatment of Asthma* which is entirely clinical.

Nor are all of the continental contributions French in origin. We should not fail to mention VanLeeuwen's *Allergic Diseases*. Incidently VanLeeuwen has written a supplementary article in *International Clinics* for June, 1927 which explains perhaps a little more clearly than does the book his conception of so-called miasmatic asthma.

Frank Coke has stressed the importance of studying asthma as an allergic manifestation as much as any other man in England. His experiences have been collected into his book on *Asthma*. This is a comprehensive exposition of the subject. The author's classification as to types is original and interesting. He classes asthma into the protein sensitization types, the thin type, the week end type, the day or night type, the type combining asthma with colds, the locality type, the periodic, the menstrual, the occupational, the drug sensitive, the bronchial type, the type associated with rapid heart, and the colloidoclasic type.

The author adds a new term, "adzyme" which to the mind of the reviewer does not clarify our understanding of anaphylaxis but which as the author suggests is for use only until a better understanding of the phenomenon has been reached. We feel that it is an unnecessary term. Another section that should interest the American reader is his discussion of vaccine therapy, particularly the method of cologenous autogenous vaccine therapy that has been developed by Danysz.

The allergist who sees any large volume of eczema or dermatitis is inclined to feel that the dermatologist pays too little attention to the possibilities of protein sensitization. R. Cranston Low, a Scotchman, has written an entire volume on the relation of allergy to dermatologic lesions and one will find considerable of interest in his *Anaphylaxis and Sensitization*. His original work presenting evidence of the development of an immunity following epidermophyton infections is especially worthy of note. The work is abundantly illustrated with many color photographs.

The otolaryngologist has in many localities been likewise slow at accepting the theories of allergy. James Adam of Glasgow has written a volume on *Asthma and Its Radical Treat-*

ment. One may anticipate his attitude in reading in the preface that "much water and more wind, mostly anaphylactic, has flowed under the bridges since the first edition was written."

The author presents his hypothesis that asthma is primarily a toxemia due in part to putrefaction and absorption from the intestines and in part to some error in nitrogenous metabolism which is closely connected with excess of carbohydrate in the diet. He claims that oxidation of the excess of the simpler carbohydrate molecule seems to interfere with proper oxidation of the more complex protein molecule. He presents no convincing experimental evidence. He discusses anaphylaxis in some detail and admits that there are some anaphylactic cases but on the whole he has little patience with the theory of allergy. Statements such as the following might bear some argument. "Idiosynerasy to feathers does occur in which case asthma usually arises when or shortly after the patient goes to bed; it has nothing to do with the attack that so suddenly comes between two and four A.M." The author marshals his evidence against allergy as the fundamental cause for asthma and this is well worth reading even though the reader may not agree with him. The aim of Adam's treatment is first to detoxicate and then to prevent toxemia by insistence on a healthy mode of life. While this is in play he attempts to reduce vagal irritability, and possible sources of irritation and of sepsis, especially in the nose are treated. He states children can nearly always be cured by attention to teeth, tonsils, adenoids, bowels and diet, exercise and cold sponging in the morning and the avoidance generally of coddling. A weekly mercurial should be given. He divides adult cases into three groups, nasal cases in which elimination of the nasal trouble will go a long way to cure; digestive cases (toxemic); and allergic cases. This third group are according to the author in a minority.

A volume of the highest value to students of bacteriology and immunology, which has just made its appearance is Jordan and Falk's *Newer Knowledge of Bacteriology and Immunology.* The editors have marshalled a great galaxy of names among the individual contributors. Among the articles in this volume which should be of especial interest to immunologists are those on the chemical structure of bacteria, bacterial oxidations and reductions, protein metabolism of bacteria, enzymes of bacteria, filterable viruses, the bacteriophage, elective localization of bacteria, bacteria of the intestinal and respiratory tracts, the immunologic basis for different types of infection by blood protozoa, the mechanism of phagocytosis, local and tissue immunity, control in standardization of biologic products, the origin of antibodies, nonspecific protein therapy, chemotherapy of bacterial diseases, and many other chapters.

Those who are acquainted with Coca's presentation of his theories of atopy as they are found for example in Tice's Medicine will be interested in his chapter in Jordan and Falk in which he briefly presents and defends his theory of atopy. Manwaring presents an extremely clear and yet brief summary of Ehrlich's side-chain theory followed by criticisms of it which more recent work has raised. Manwaring's own enzyme theory which he proposes as a substitute is not followed as easily as is his presentation of Ehrlich's theory.

Another recent volume into which allergy enters only incidentally but which is full of information and facts for the immunologist is the work on *Filterable Viruses* edited by Rivers.

Those who are interested in serologic investigations and the humoral aspects of immunity will find considerable of interest in Browning's *Immunochemical Studies.* This is a compilation of work done mainly in the pathological department of the University and Western Infirmary, Glasgow, and deals with investigation in the nature of antigen, antibody and complement.

Those who are delving into the possibilities and the results of clinical immunization against the bacterial diseases will find in Robertson's *Therapeutic Immunization* a presentation of the author's wide experience and conclusions. Methods are described in quite minute detail.

Very good information on vaccines and biologic implements of therapy is to be found in Solis-Cohen and Githens' *Pharmaco-Therapeutics.* The senior author presents in detail his technic and the theoretical considerations in connection with his *selective pathogen culture*

method. A great deal of information is to be found in this volume also on the pharmacodynamics of calcium and other inorganic ions. For information on biologic therapy Kolmer's monumental work should not be overlooked.

Works on Vital Processes

The student of allergy is a student of vital activity. Allergy does not occur in dead substances. The phenomena of anaphylaxis, immunity and allergy are abnormal manifestations of vital activity. For an intimate understanding of these manifestations one must have a well grounded understanding of normal activity. The following works are suggested for this purpose.

Bayliss' *Colloidal State* is an excellent introduction to an understanding of colloidal chemistry in its medical and physiologic aspects. We might term it the A. B. C. of colloidal chemistry.

A series of lectures on *Biologic Aspects Colloidal and Physiologic Chemistry* has been published in book form by The Mayo Foundation. The first chapter contributed by Robert A. Millikan deals with Principles Underlying Colloid Chemistry. Martin Fisher contributes a chapter on Colloid Chemistry in Biology and Medicine. Robert Chambers writes on the Physical Properties of Protoplasm. Ross A. Gortner tells of Adsorption and Vital Phenomena. E. Franklin Burton covers the Physics of the Ultramicroscope and the Optical Properties of Colloid Particles. The last chapter by William T. Bovie deals with the biologic effects of life.

Dr. Robert Chambers also has an excellent paper on *The Nature of the Living Cell as Revealed by Microdissection* in *The Harvey Lectures*, Series 22, 1926-27. In this same volume is a brief but excellent discussion on *Organic Chemistry*, its relation to medicine by Dr. Richard Willstatter of Munich.

There is a volume which should be in the hands of every student of vital activity. This is *General Cytology* edited by Edmund V. Cowdry. Three chapters in particular deal with the subject under consideration. These are *Some General Considerations of the Chemistry of Cells* by Albert P. Matthews; *Permeability of the Cell to Diffusing Substances* by Merle H. Jacobs and *Reactivity of the Cell* by Ralph S. Lillie.

A companion work to General Cytology, *Special Cytology*, edited again by Cowdry is the best reference work available on the histology, embryology and function of differentiated cells such as are found in the various tissues of the living body. For the purpose of the present review we would recommend particularly the chapters on the Special Cytology of the Skin, the Mucous Membrane of the Respiratory Tract, the Intestinal Epithelia, the Liver, the Reticulo-endothelial System and the various types of leucocytes in the circulating blood.

Willstatter, mentioned above, has contributed a brief but instructive orientation monograph on *Problems and Methods in Enzyme Research.*

We must remember that in allergy and anaphylaxis we are dealing not only with the vital activity of the host but also with the biologic or vital activity of the antigens and that the biochemistry of the latter must also be studied. Buchanan and Fulmer have written a monumental work on *Physiology and Biochemistry of Bacteria* which contains a wealth of information but is very highly technical and therefore rather difficult of digestion.

Allergy—Asthma, Hay Fever, Urticaria and Allied Manifestations of Reaction, by William W. Duke, Ph.B., M.D., Kansas City, Mo. 339 pages. Cloth. With seventy-five illustrations. C. V. Mosby Co., St. Louis, Mo. 1925.

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EDITORIALS

The Nature of Bacteriophage

THE observation by Twort in 1915 and d'Herelle in 1917 of transmissible lysis in bacteria constituted a phenomenon of such novelty that nearly all bacteriologists have interested themselves deeply in its study. Many have carried their investigations to great length and have contributed abundantly to our knowledge of the process, but so far none has reached a generally accepted understanding of its mechanism. Nearly every man who has conducted extensive observations in this field has offered his own theory so that theories there are aplenty but there are none against which other observers have not raised serious objections.

D'Herelle believes that the lytic principle is a foreign filterable virus which parasitizes bacteria, destroying them by lysis. He looks upon bacteriophagy as a contagious disease of bacteria. The infecting agent is an ultramicroscopic filterable corpuscle multiplying at the expense of young living bacteria some of which latter may acquire an immunity to the parasite becoming resistant to its lytic action.

Kabeshima was probably the first to disagree with d'Herelle and suggested that the lytic agent was a catalyzer produced by the digestive glands,

possibly also by leucocytes which activated a diastase normally present in the bacterial cells, the latter causing destruction of the cell. This view has few adherents.

A rather widely favored explanation was formulated by Bordet and Ciuka in 1920 who believe that the essential process is an autolysis resulting from a rupture of the equilibrium existing in the living bacterium between assimilation and metabolism. This is spoken of as a nutritive vitiation. With a breaking of the balance between anabolism and catabolism the bacteria undergo self-destruction. The products of this autolytic destruction are toxic for other bacteria in the culture and when liberated incite autolysis in neighboring bacteria, thus making the lytic process transmissible. A criticism of this theory which appears to have considerable weight in that most of the evidence so far adduced tends to confirm d'Herelle's original assumption that the bacteriophagic principle is particulate in nature and is not a substance in solution. Moreover, there is some criticism of the manner in which Bordet and Ciuka explain the origin of the lytic principle. They obtained it through the action of leucocytic exudate of guinea pigs after intraperitoneal inoculation of B. coli. They suggested that the exudate releases the lytic action. But as Bronfenbrenner and others have pointed out bacteriophage appears to be as universally distributed as bacteria themselves, and it is difficult to establish that no bacteriophage was introduced into cultures along with the leucocytic extract. Bordet and Ciuka believe that bacteriophage is an autolysis arising in the bacteria from vitiated metabolic activity probably originally incited by some as yet hypothetical external influence but capable of self-propagation because of the toxic stimulative action on other cells of these liberated autolytic products.

Most investigators agree with d'Herelle that bacteriophage is corpuscular and has definite mass, the estimated diameter ranging from twenty to ninety millimicrons or about the size of a protein micella. Not so many have agreed that d'Herelle has positively established his conception that bacteriophage is actually a living substance. He believes that he has demonstrated that it possesses powers of environmental adaptation, of propagation and of metabolic assimilation in a heterogeneous medium. But other explanations for his conclusions have been suggested and the question whether bacteriophage is a living reproducing extra bacterial substance has not been settled.

Kuhn in 1919 made a careful microscopic study of certain bacterial forms present in cultures, which appeared swollen and contained small granular bodies which he called Pettenkofer bodies. After further study in 1926 he stated his belief that these bodies were a virus living in symbiosis with the bacterial cells, thus aligning himself more or less with d'Herelle. He states that he has seen the minute granules or spores, liberated after the bursting of the swollen bacteria, attach themselves to new bacteria. This parasite according to Kuhn belongs in the classification of myxomycetes.

Koch and Ziegenspeck have made somewhat similar observations and reached very much the same conclusion.

Beguet has proposed an osmotic theory of bacteriophagy. Some bacterial cells, the so-called sensitive cells, absorb colloid from the surrounding medium increasing their osmotic pressure so that they swell and burst. This bursting liberates larger amounts of colloid material in the neighborhood of adjoining bacterial cells and the latter proceed to repeat the experience of the former. The osmotic equilibrium existing between the germ and the absorbed colloid or the colloids present in the medium is disturbed. Some cells are destroyed by an excess of internal pressure while others can adapt themselves to a lower pressure thereby becoming resistant.

This theory has not gained great favor. As Hadley says, such theories take undue liberties with our present knowledge of physical chemistry as applied to colloids in the bacterial cells and the power of absorption from the medium. "One might almost come to believe after reading such a presentation as that of Beguet that the living micro-organism is merely a toy, existing only to be played on by its colloidal environment, rather than a biologic entity possessing in itself an inherent directive mechanism."

Wollmann believes that the lytic element arises within the bacterial cell. In his earlier work he suggested that the reaction of bacteriolysis is due to corpuscular elements which arise from the bacterial cells themselves and are transmissible from mother cell to daughter cell or perhaps from affected cell to normal cell through the external medium. In this we find a suggestion of an hereditary tendency which may be transmitted in the offspring but not only in this way but also from one mature cell to another mature cell across an intervening environment. This is indeed a new idea.

More recently Wollmann has elaborated on his theory of hereditary factors. Wollmann believes that the hereditary factors are corpuscular in nature and that while they arise within the bacterial cell they may exist outside of the cell, thus developing a certain degree of autonomic activity and may produce in other normal cells the modifications of which they are the bearers.

Wollmann's hypothesis might be described as a cross between that of d'Herelle and that of Bordet and Ciuka. He calls into play an extracellular living corpuscular element but one which originates in the metabolic activity of the bacterial cell and incites similar metabolic derangement or rupture of equilibrium between anabolic and catabolic function in neighboring cells. The difficulty with the acceptance of this theory is the conception of the transmission of acquired hereditary factors through the external environment and the conception of a fragment or portion of the living cell taking on an autonomous existence so that it can continue to live outside of the dead cell.

Hadley suggests yet another hypothesis, one which he admits is yet unproved but has much in its favor and should be considered as a possibility when attempting to explain the results of any new experimental observations. This author aligns himself with those who believe that the evidence favors a living nature for the bacteriophagic principle. On the other hand he is inclined to accept the evidence that transmissible lysis may appear in a bacterial culture in which the possibility of introduction of bacteriophage from the outside has been completely eliminated. His conclusion is then that the

bacteriophage is a living corpuscular extracellular substance which arises from the normal living bacteria. With this as a start he elaborates his microbic dissociation theory.

Briefly, Hadley believes that reproduction in bacteria is by no means as simple a thing as the ordinary fission with which all are familiar. He presents the accumulated evidence suggesting that there may at times be a sexual form of reproduction in which complete living bacterial units assume forms, sometimes very minute forms, which have in the past been generally unrecognized. In support of this he mentions such phenomena as the passage of granular forms of the tubercle bacillus and of other bacteria through porcelain filters and states that with some bacteria repeated reculturing of these ultramicroscopic granular forms and probably together with certain environmental alterations in the media, sometimes causes the cultures to revert back to the original "normal" bacterial form. That bacterial multiplication is not merely a matter of simple fission is suggested by his list of accessory means of reproduction: (1) conjugation and zygospore formation, followed by endosporulation; (2) gonidia formation (macrogonidia and microgonidia); (3) a process of budding which may or may not be related to the formation of gonidia; (4) propagation through the formation of symplaste aggregates (the "bacterial plasmodium" of Almquist).

Hadley's suggestion is that bacterial dissociation into its less typical forms occurs normally, particularly under specific environmental alterations. The environmental changes being kept constant there is no reason why the bacterial mutation should not persist, only to be changed again when the surrounding medium becomes changed to a less propitious state.

Hadley then would attribute the change to an alteration originating within the bacterial cell. Bronfenbrenner on the other hand states that during the last four years he has attempted repeatedly by various procedures to induce the spontaneous appearance of phage in a variety of cultures known to be free from phage. So far the results have been consistently negative. He does state, however, that recently Fukuda reports having succeeded in inducing spontaneous production of phage in cultures of known purity.

There are many other hypotheses that have been suggested as explanations for the phenomenon of transmissible lysis. It has been suggested that bacteriophage resembles a growth hormone or exhibits cytotoxic properties and causes such an increase of metabolic activity in the bacteria that lysis occurs as a terminal stage of this trophic disease. Another suggestion is that with the abnormally rapid rate of bacterial growth the amount of proteolytic enzyme set free by the bacteria is so great that the supply of protein is exhausted and the ferments attack the bacteria themselves.

Bail's hypothesis closely resembles that of Wollmann. According to him, autolysis is due to the loss by the bacterial chromosomes of their anabolic function. The cells with imperfect chromosomes possessing only the function of catabolism undergo dissolution. The imperfect chromosomes are thereby set free and are capable of initiating similar vitiation in other bacteria.

There are yet other theories which have few or no adherents other than their originators.

In summarizing the evidence pro and con, Hadley, who is not an advocator of d'Herelle's theory, writes as follows: "Bordet stated two years or more ago that d'Herelle would soon be left as the sole supporter of his virus theory. This is undoubtedly true for it is seldom now that one encounters further reports of a sustaining nature. In this regard, however, it is a curious and unfortunate circumstance that the loss of prestige of d'Herelle's view has not followed the actual disproof of any of his splendid array of facts nor has it followed the setting up of counter proof. It seems to have been determined largely by that poorly defined and scarcely scientific feeling of 'general improbability.'" Elsewhere he says, "At present it must be frankly admitted that d'Herelle's theory is the one that explains most satisfactorily the greatest number of observed facts. Moreover, the theory is so strongly fortified that it can never be disproved by resort to juggling and to reinterpreting the facts that he has presented for he has contributed the only possible interpretation of this body of facts as they now stand. In other words the disproof of d'Herelle's view as also of the theory of Bordet and Ciuka depends entirely on the accumulation and analysis of new facts."

Bronfenbrenner states, "Although facts concerning the phenomenon of bacteriophagy leave an impression that the active agent of transmissible lysis is a bacterial product, the reports concerning the successful production of phage from bacteria without the intermediary of other biologic materials have thus far not been entirely convincing."

At the present time any survey of the field of hypotheses explaining transmissible lysis must be presented from an agnostic point of view. We know that the phenomenon exists but so far we possess no invulnerable theory regarding the mechanism of its production.

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—*W. T. V.*

Erratum

In the article by Edward Hollander, entitled *Studies in Biliary Tract Disease,* June issue, page 863, seventh line, "30 c.c. of 25 per cent magnesium sulphate" should read "30 c.c. of 33 per cent."

In the sixth line of the legend on page 865, "30 c.c. of 25 per cent magnesium sulphate" should read "30 c.c. of 33 per cent."